From MEDICAL EPIDEMIOLOGY AND BIOSTATISTICS
Karolinska Institutet, Stockholm, Sweden

Socioeconomic factors and the influence of comorbidity in the management and survival in lung and prostate cancer

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Stockholm 2012

Published by Karolinska Institutet. Printed by Universitetsserivce US-AB, Stockholm.

ISBN 978-91-7457-651-1

"You can observe a lot just by watching"

Lawrence Peter (Yogi) Berra

To my family
Snjezana, Saga and Axelia

ABSTRACT

Socioeconomic factors and the influence of comorbidity in the management and survival in lung and prostate cancer

Aim: The presence of co-existing disease is common in cancer patients, and for many cancer forms outcomes are associated with socioeconomic status. The present thesis aimed to explore possible associations between socioeconomic status and comorbidity on the one hand, and clinical management and survival on the other hand, in patients diagnosed with lung and prostate cancer.

Methods: In study I, 3,370 patients diagnosed with non-small cell lung cancer between 1996 and 2004 were identified in the Regional Lung Cancer Register in central Sweden with additional information obtained from other population based registers. Study II encompassed 15,518 patients diagnosed with lung cancer identified in the Thames Cancer Register in South East England between 2006 and 2008. A total of 17,899 high risk prostate cancer patients (Study III) and all 77,536 men diagnosed with prostate cancer (Study IV) between 1997 and 2006 were identified in PCBaSE Sweden, a database of prostate cancer patients based on the National Prostate Cancer Register of Sweden with additional information retrieved from other population based registers. Level of education, a deprivation index, and a socioeconomic index based on occupation were used as the main indicators of socioeconomic status. Comorbidity burden was assessed using the Charlson comorbidity index. Binary logistic regression and time to event analyses were used to address associations between socioeconomic status, comorbidity, management and survival.

Results: We observed social differences in time between referral and date of diagnosis and in diagnostic intensity in lung cancer patients in Sweden. No social differences in stage at diagnosis were observed in Sweden or in South East England. In both regions the most privileged lung cancer patients were more likely to receive treatment with curative intent and had a better survival, foremost in early stage disease. We observed socioeconomic disparities the management of high risk prostate cancer. The likelihood to undergo a bone scan, receive curative treatment, and undergo radical prostatectomy was higher in patients with high socioeconomic status, a group that experienced a lower mortality. Prostate cancer patients with severe comorbidity received curative treatment less often, had a higher all-cause and competing cause mortality, but not higher prostate cancer specific mortality. However, in analyses given no death from other causes, men with severe comorbidity had a higher prostate cancer specific mortality.

Conclusions: Taken together, the results of the present thesis show that socioeconomic status influences not only clinical management, but also survival in patients diagnosed with lung cancer both in central Sweden and South East England, as well as in Swedish patients with high risk prostate cancer. Comorbidity burden influenced both treatment decisions and mortality in prostate cancer patients. The pattern of care and survival observed in the most privileged groups demonstrates what is achievable and should represent a minimum standard for all cancer patients.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals:

I. **Berglund Anders**, Holmberg Lars, Tishelman Carol, Wagenius Gunnar, Eaker Sonja and Lambe Mats. Social inequalities in non-small cell lung cancer management and survival: a population-based study in central Sweden.
Thorax. 2010;65(4):327-33.

II. **Berglund Anders,** Lambe Mats, Lüchtenborg Margreet, Linklater Karen, Peake D. Michael, Holmberg Lars and Møller Henrik. Social differences in lung cancer management and survival in South East England - the role of patient, clinical and treatment factors.
Submitted.

III. **Berglund Anders**, Garmo Hans, Robinson David, Tishelman Carol, Holmberg Lars, Bratt Ola, Adolfsson Jan, Stattin Pär and Lambe Mats. Differences according to socioeconomic status in the management and mortality in men with high risk prostate cancer.
Eur J Cancer. 2012;48(1):75-84.

IV. **Berglund Anders**, Garmo Hans, Tishelman Carol, Holmberg Lars, Stattin Pär and Lambe Mats. Comorbidity, treatment and mortality: a population based cohort study of prostate cancer in PCBaSe Sweden.
J Urol. 2011;185(3):833-9.

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LIST OF ABBREVATIONS

CCI	Charlson comorbidity index
CI	Confidence interval
CT	Computerized Tomographic
DRE	Digital rectum examination
GnRH	Gonadotropin-releasing hormone
HR	Hazard ratio
ICD	International Classification of Diseases
LISA	Longitudinal integration database for health insurance and labor market studies
MRI	Magnetic resonance imaging
NHS	National Health Service
NPCR	National Prostate Cancer Register
NSCLC	Non-small cell lung cancer
OR	Odds Ratio
PCBaSE	Prostate Cancer Database Sweden
PET	Positron emission tomography
PSA	Prostate specific antigen
RCC	Regional Cancer Center
RLCR	Regional Lung Cancer Register
SCLC	Small cell lung cancer
SCR	Swedish Cancer Register
SEI	Socioeconomic index
SES	Socioeconomic status
sHR	subdistribution Hazard Ratio
TRUS	Trans-rectal ultrasonography
WHO	World Health Organization

1 INTRODUCTION

Worldwide, lung cancer is the most common malignancy, and is also the leading cause of cancer death globally among men. Among women, lung cancer is the fourth most common cancer and the second leading cause of cancer death globally. In Sweden, more than 3,200 incident lung cancer cases are diagnosed each year. Prostate cancer is the second most frequent malignancy in men and the sixth leading cause of cancer death globally. In 2009, more than 10,000 men were diagnosed with prostate cancer in Sweden, which makes it the most common cancer in men in Sweden.

The Swedish national health care system aims to provide high quality care to all residents on equal terms. In an international perspective, cancer care in Sweden is of high quality and prospects for survival are better and cancer mortality is lower compared to many other countries. However, despite an improved understanding of etiological factors, and progress in treatment there is a need to further improve the management of cancer patients. Several countries have launched national cancer plans, because of an expected dramatic increase in the burden of cancer due to ageing populations. Another concern has been to understand and to reduce geographical and social variations in access to cancer care, management and survival. A new Swedish national cancer plan was introduced in February 2010.

In recent years, there has been an increased interest in cancer research in the United Kingdom, partly because of poor national outcomes compared to other countries, including Sweden. In 2000, England published a cancer plan that aimed to improve prevention, early diagnosis and screening, treatment and survival. There is compelling evidence of socioeconomic disparities in cancer survival in England and Sweden, as well as in many other countries. Both the Swedish national cancer strategy and the English cancer plan included strategies to reduce inequalities in cancer survival.

The origins of observed disparities remain, however, largely unknown. Contributing factors are likely to include those related to the tumor, the host and the health care system. In this context, it could be hypothesised that tumor characteristics may be influenced by exposures associated with socioeconomic standing and that life-style factors influence general health status, host defence and their ability to tolerate the treatment. Further, that the knowledge a patient has about cancer and its treatment influences health care selection behaviour and compliance; and that both overt and subtle processes linked to socioeconomic standing affect access to state-of-the-art treatment.

Demographic changes with increased longevity and rapidly aging populations are expected in Sweden and in the rest of the world. The number of elderly men and women diagnosed with cancer will increase dramatically in a near future. The number of men with cancer in Sweden in year 2030 has been estimated to be 130 percent higher than in 2006. Lung cancer will continue to increase in women, a change that reflects smoking habits during the late 1960s, 70s and 80s. Since most patients that are diagnosed with cancer at an older age have several comorbidities, it will be increasingly important to consider co-existing disease in the clinical management of cancer.

The aim of the present thesis was to investigate possible associations between socioeconomic status, comorbidity, management and survival in lung and prostate cancer patients identified in population based registers in Sweden and South East England.

2 BACKGROUND

2.1 Socioeconomic inequalities in health

Social epidemiology is defined as "the branch of epidemiology that address the social distribution and social determinants of health" [1], that is, "both specific features of, and pathways by which, social conditions affect health" [2]. More precisely, the focus of social epidemiology is to address the ways in which a person's position in the social structure influences the likelihood that he or she will develop or survive from the disease [1]. The effect of social 'class' (a summary term for various socioeconomic factors, such as occupation, education, income, et cetera) in relation to mortality has been addressed since the nineteenth century. An English study developed methods for social classification and revealed major socioeconomic differences in mortality rates already in the 1860's [3]. The dramatic decline in infectious diseases before the development of modern pharmaceuticals has been attributed to changes in social conditions that included nutrition, sanitation and general living conditions [4], but also to specific public health interventions, where urban congestion may have played a major role [5].

Great Britain has a long tradition regarding of research social inequalities in health. A landmark publication was the Black report published in 1980, which concluded that "from birth to old age, those at the bottom of the social scale have much poorer health and quality of life than those at the top" [6]. This conclusion may apply to other countries than Great Britain and to a variety of health indicators [7]. The Black report denoted Sweden as a country with almost no difference in health. However, at that time this conclusion was based on very sparse data.

Socioeconomic inequalities in mortality have previously been reported in several populations [8-14], independent of the socioeconomic indicator used [15]. Low socioeconomic status has been associated with a higher mortality from cardiovascular disease, diabetes and cancer. Converging evidence from studies conducted in Sweden has shown that lower socioeconomic status is associated with higher prevalence of health complaints, many chronic conditions and adult mortality [16]. Findings from Weires et al. showed that higher socioeconomic status was associated with a lower overall and cause-specific mortality in Sweden [17]. A detailed analysis by Shkolnikov et al. demonstrated increasing disparities in absolute mortality in relation to level of education in Sweden. Similar patterns have also been observed in Norway and Finland between 1971 and 2000 [18]. The magnitude of social gradients in health is similar in different European countries, although the mechanisms underlying these variations may differ. One study concluded that the social inequalities in self-rated health were similar in Sweden and Great Britain, but the distribution of income across occupational social classes explained a larger part of the observed inequalities in Britain than Sweden, which may reflect differences in low income and poverty [19].

2.2 Socioeconomic inequalities and cancer

Cancer is a term that defines a large group of diseases, all of which involve unregulated cell growth. Cancer cells can spread to more distant parts of the body through the lymphatic system or blood stream. The risk of developing cancer generally increases with older age [20], but cancer can affect people of all ages. Only a few malignancies are more common in children than in adults. The prognosis is greatly influenced by the *type* and *location* of the cancer and the *extent* of disease at the time of diagnosis.

The importance of studying associations between socioeconomic factors and cancer has been discussed in several studies [21]. It has been established that there are social class differences in incidence and mortality from cancer [22], differences which appear to have increased, in relative terms, compared to the nineteenth century [23 24]. For most cancer sites, converging evidence indicates that the risk is almost twofold when comparing the most disadvantaged group with the most advantaged group [25].

The Swedish National Board of Health and Welfare recently reported that the association between socioeconomic status and the overall risk of cancer has changed over time for males, where men with high socioeconomic status had a higher incidence in the beginning of the 1990s, while no clear differences were observed in the later calendar periods [26]. In women, the incidence of all cancer sites was independent of socioeconomic status between 1989 and 2009. The overall cancer incidence for men for all cancer sites increased from 969 to 980 per 100,000 person years between 2007 and 2009. The corresponding incidence for women increased from 765 to 768 per 100,000 person years. The incidence of melanoma, prostate cancer for men and breast cancer for women was higher for patients with high socioeconomic status compared to those with low socioeconomic status, while the incidence of lung and cervical cancer shows the reverse trend. This has been observed in several countries [22 27-29], including earlier studies based on Swedish data [21 30-32]. The observed differences in the incidence may be explained by differences in risk factors such as smoking and ultraviolet radiation, as well as prostate specific antigen testing and frequency of mammography screening [33-36]. Since prostate and breast cancer are the two most common cancer sites for men and women in Sweden, respectively, this explains why no social differences are observed for all cancer sites combined.

A longitudinal study concluded that educational differences in cancer mortality existed among men and women in the 1990s, but also that mortality varies by sex, and differs between cancer sites across Europe [37]. However, the social inequalities in all cancer combined appear to be much smaller in Sweden, Norway and Denmark in comparison to other European countries, which in part may be explained by differences in the distribution of cancer sites across countries.

If studies are restricted to the social class distribution of cancer mortality, results may be biased if cancer survival is also linked to socioeconomic position. For instance, in a social group with a relatively high probability of survival after diagnosis the event of death will tend to be postponed. Consequently, their mortality will appear relatively low even if the incidence of the disease is identical with that of a comparison group [21]. Thus, to understand

the role of socioeconomic differences in early detection and treatment of cancer, it is fundamental to also address socioeconomic status in relation to cancer survival [21].

In 1955, Cohart et al. reported an association between socioeconomic status and breast cancer survival [38]. Results from subsequent research have established that there is a clear social pattern in cancer survival [21 39]. These social differences tend to occur foremost in cancers that have good prognoses, where the stage at diagnosis is a key prognostic factor [21 39]. In 1987, Vågerö et al. documented social disparities in cancer survival in Sweden using information available in the Swedish Cancer Register [40]. In that study, the cumulative survival was higher in patients with high social class for all cancer sites combined, as well as for specific sites such as breast, cervical and rectal cancer, while no social differences in survival were observed for lung, stomach and pancreatic cancer. A recent Swedish study concluded that socioeconomic differences in patient survival have increased over calendar time for acute myeloid leukemia and multiple myeloma [41]. During the last two decades there has been an increased interest in identifying possible explanations for the observed social differences in cancer survival, which has led to more detailed analyses including information on clinical characteristics and management. A population based study in Sweden found that social gradients in breast cancer survival remained following adjustment for clinical characteristics and treatment factors [42].

Possible explanations for the social differences in cancer survival have been discussed in several studies. In 1977 Berg et al. suggested that when there are no differences in treatment, socioeconomic variations in survival might be due to differences in when medical help is sought, in the general health and life expectancy of the patients, or in the cancer-host interaction and the behavior of the cancer [43]. In 1987, Vågerö et al. provided a list of explanations of inequalities in survival, including roles for factors related to the tumor, the patient and the health care system [40].

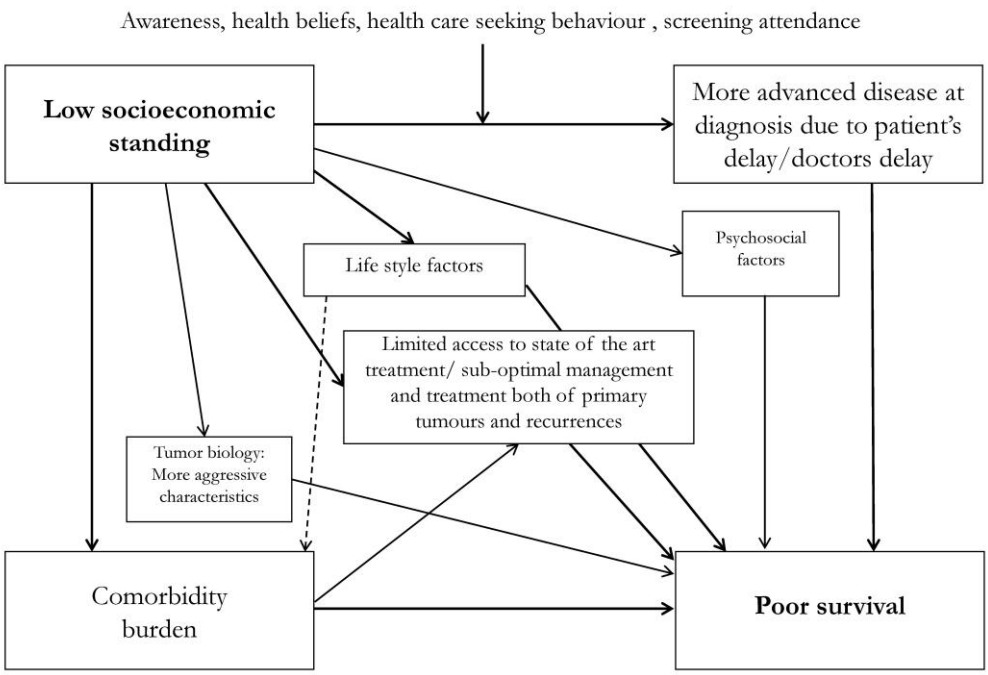

Figure 2.2.1 *Possible pathways underlying socioeconomic differences in cancer survival (Source: adapted from Franco EL. Epidemiology as a tool to reveal inequalities in Breast Cancer Care [44])*

Figure 2.2.1 illustrates possible pathways underlying socioeconomic differences in cancer survival. Social differences in stage at diagnosis have been an attractive explanation since it represents a key clinical prognostic factor. It has also been suggested that differences in histological type of the tumor may explain part of the observed social inequalities [21 39].

Another explanation put forward is that an impaired host resistance among patients with low socioeconomic standing would lead to a more rapid tumor growth and spread. Life style factors such as physical inactivity, poor nutritional status, obesity, tobacco smoking and alcohol consumption are related to low socioeconomic status and may contribute to an impaired host resistance. A recent study show that cancer patients with low socioeconomic status have a higher prevalence of co-existing diseases which is associated with higher all-cause mortality [45].

Since cancer survival is highly dependent on diagnostic procedures and choice of treatment, it has been suggested that survival inequalities reflect differences in the clinical management. Moreover, the health care provider's attitude with regard to management may reflect aspects of physician-patient interactions, including a subtle bias towards more action on behalf of the physician when treating patients with high socioeconomic status.

2.3 Health care systems

2.3.1 An overview of the Swedish health care system and the cancer strategy

Sweden is geographically the third largest country in Western Europe, has a population of 9 million and is divided into 21 counties and 290 municipalities. There is no hierarchical relation between the counties and the municipalities, which all have their own self-governing local authorities. Municipalities are responsible for matters relating to their residents and the immediate environment. The main task of the county councils is health care, which accounts for around 90% of the county councils' activities [46].

According to Swedish law, all residents have an equal right to healthcare services independent of sex, age, ethnicity, socioeconomic status or residence. The life expectancy in Sweden is high; in 2010 it was 83 and 79 years for women and men, respectively [47]. With over five percent of the population aged 80 years or older, Sweden has the largest proportion of elderly in that age bracket in Europe.

While the health care system in Sweden is highly decentralized, national health policy is a responsibility that rests with the Government and the Parliament. The Swedish arrangement is a national health system, funded through county and municipal taxes, and used by virtually all residents augmented by a limited range of care services by private interests. All counties and many municipalities contract to varying degrees with private providers, mainly in primary care where approximately ten percent of the primary care centers were managed privately in 2007. Thus, compared to other countries, the Swedish health care system is relatively unified, with county councils and municipalities serving as the primary providers.

In an international comparison, the Swedish health services are of high quality judged on accessibility of care, resource and cost levels, range of health care services provided and good medical outcomes (e.g. low mortality from cancer). However, compared to other countries in the European Union, cancer care in Sweden achieved only a middle ranking with regard to the population' satisfaction [46]. The Swedish national cancer strategy introduced in February 2010 [48], addresses several key areas of importance to improve cancer care in Sweden. There are five overall goals:

- To reduce the risk of developing cancer
- To improve the quality of cancer management
- To prolong survival times and improve quality of life after a cancer diagnosis
- To reduce regional differences in survival time after a cancer diagnosis
- To reduce differences between population groups in morbidity and survival time.

One key component of the national cancer strategy is to develop six regional nodes, Regional Cancer Centers (RCC), in each of the six large health care regions in Sweden [49]. The aims for the RCCs are:

- To formulate and implement a strategy to reduce the risk of developing cancer.
- To lead and coordinate the cancer care processes within the six health care regions
- To implement a strategy that assures the provision of psychosocial support to cancer patients
- To strengthen the patient's role during the management of the disease
- To take a leadership role in the medical training and recruitment of a cancer workforce
- To participate in the implementation of national guide lines, and to use information from the national cancer quality registers to ensure high quality cancer care
- To efficate knowledge transfer between clinical research and cancer care, and to increase research collaboration between the councils, universities and the industry
- To have a clear leadership role with strong support from the councils, and to collaborate with the other RCCs
- To develop a strategic plan to improve the cancer care in the health care region
- To develop and implement a strategy for "level structuring" of cancer care within the health care region.

The six RCCs are expected to collaborate as well as with similar organizational bodies in other countries. The RCCs will utilize information from quality registers, health registers and other population based registers both for quality control and research.

2.3.2 An overview of the National Health Service in England and the cancer plan

The health care system in England is mainly built on the National Health Service (NHS) that provides health care to all permanent residents in the United Kingdom. Within this system, health care is free at the point of use and paid for from general taxation. The NHS provides the majority of health care in England, including primary care, in-patient care, long term health care, ophthalmology and dentistry. Since the start of NHS in 1948, private health care has developed in parallel. It is paid for largely by private insurance, but is used by less than eight per cent of the population and generally as a top-up to NHS services.

In England more than 200,000 people are diagnosed with cancer, and around 120,000 people die from the disease annually [50]. Several studies show that cancer survival rates are lower in England than other countries in Europe [51-54]. In July 2000, a national cancer plan was introduced with the goal to support prevention and to improve cancer management for all patients [55]. More specific aims were to save more lives, to ensure the right to professional support and care based on the best treatment available, to reduce inequalities in incidence, mortality and survival, and to build the future cancer workforce through strong clinical cancer research.

2.4 Population based records and quality registries in Sweden

Sweden has a long history of population based records. In the 17th century the church gathered information with the aim to collect taxes and to identify men eligible for military service [56]. In 1749, a nationwide reporting system for cause of death was introduced, which was in 1951 adapted to standards of the international World Health Organization [57]. During the 1960's population records were computerized and in 1967 a check digit was added to an individually unique personal identity number that had been introduced in 1947.

Administrated by the National Board of Health and Welfare, the Swedish Cancer Register was founded in 1958 [58]. The recording of incident cancer cases is mandatory by Swedish law with the primary aim of monitoring cancer incidence and mortality trends. However, to fill the gap left by the lack of primary monitoring variables such as clinical characteristics, mode of detection, diagnostic procedures and treatment modalities in the Swedish Cancer Register, cancer quality registers have been increasingly used for quality control and research. Currently there are 25 national cancer quality registers that contain detailed information on demographic factors, clinical characteristics and aspects of management [59]. These databases are extensively used for local, regional, and national monitoring of cancer care. Research based on quality registers is often focused on long-term outcomes and possible causes of differences in cancer survival. The quality registers are also used to identify groups of patients that can be studied in more detail to improve the understanding of tumor biology.

2.5 Survival analysis

Survival analysis from population based studies may have different interpretations for different audiences. Survival estimates based on population based studies are in general lower than survival rates obtained from clinical trials. For clinicians, the population based estimates can be used as an approximate benchmark for cancer patient survival [60]. For policy makers, an improved survival rate implies that resources need to be allocated to subsequent treatment, monitoring, and palliative care for surviving cancer patients [60]. For the general public, both cancer incidence and survival may appear more relevant than mortality since they relate to groups that still are alive [60]. There are several factors, such as comorbidity and socioeconomic status that might distort the interpretation of survival differences between patients from various groups. Other factors of importance include completeness, quality and validity of the information available in population based registers.

2.6 Lung cancer

Lung cancer is a disease characterized by uncontrolled cell growth in tissues of the lung **(Figure 2.6.1)**, and most lung cancers are carcinomas that derive from epithelial cells, in the bronchial tree.

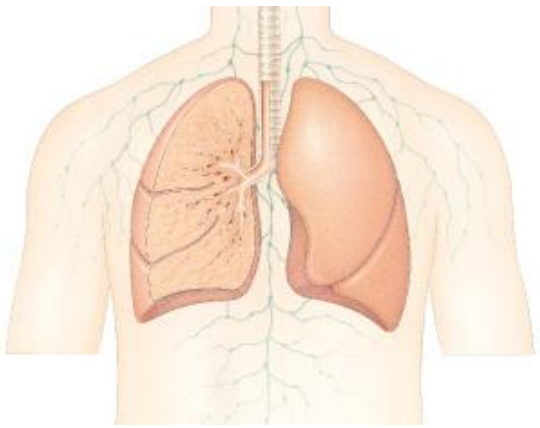

Figure 2.6.1 *Anatomy of the lungs (Source: Swedish Cancer Society, illustrated by Roland Klang)*

Lung cancer is one of a few cancers for which one main risk factor has been identified. Following the first reports in the 1950s, epidemiological studies have demonstrated with overwhelming evidence that tobacco smoking causes lung cancer [61]. Tobacco smoking is estimated to account for 80% of the worldwide lung cancer burden in men and at least 50% for women [62 63]. Lung cancer is today the most common malignancy in the world, with an estimated 1.61 million incident cases in 2008, representing 12.7 % of all cancers diagnosed in that year [64].

In 2008, the age standardized incidence rates of lung cancer was generally higher in men compared to women **(Figure 2.6.2)**. Among men, the highest incidence rates of lung cancer were observed in North America, Europe, Asia and Australia. The highest incidence rates for women were found in North and South America, Europe, Australia and China.

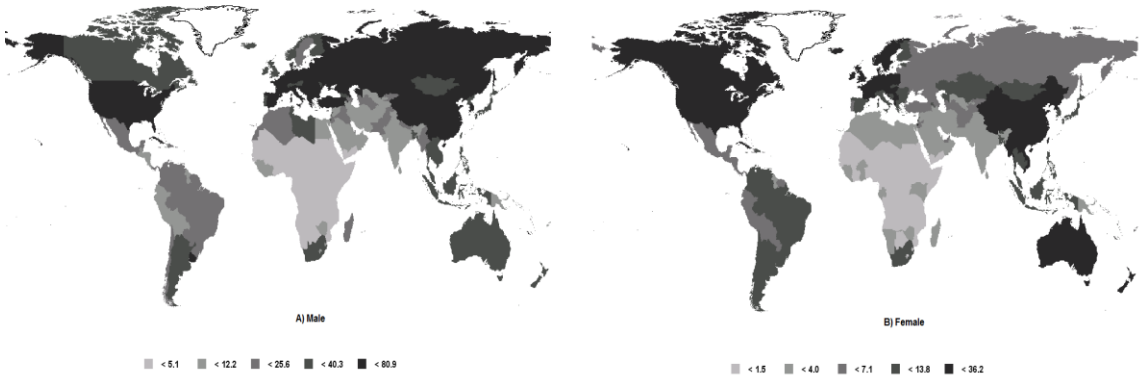

Figure 2.6.2 *Age standardized incidence rates of lung cancer per 100,000 for A) men and B) women in 2008. Dark colored areas have the highest incidence rates, whereas the areas with the brightest color have the lowest incidence (Source: GLOBOCAN 2008)*

More than 3,200 people in Sweden and more than 40,000 in England receive a lung cancer diagnosis each year [65-67]. Between 1980 and 2008, the European age standardized incidence of lung cancer rates per 100,000 among men decreased from 113 to 59 in England and from 39 to 31 in Sweden [66 68]. The opposite has been observed for women, where the incidence rates during the same calendar period increased from 28 to 39 and from 12 to 26 per 100,000 in England and Sweden, respectively. The gender-specific incidence rate patterns are

likely to be explained by the long time lag between exposure to risk factors for lung cancer, primarily smoking and the development of the disease. Smoking patterns in Sweden have changed dramatically during the last decades. Between 2004 and 2008, smoking among women decreased from 19% to 14%, whereas the proportion of men that smoked on regular basis decreased from 14% to 11% [69].

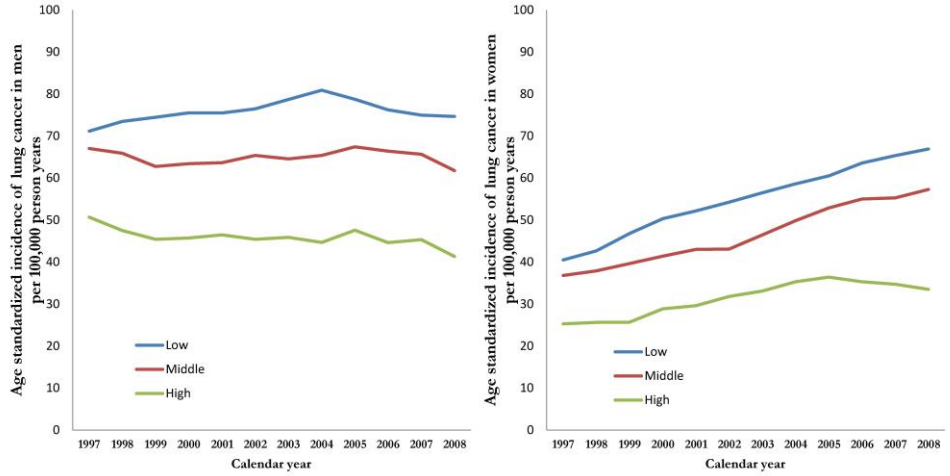

Figure 2.6.3 *Age standardized incidence of lung cancer per 100,000 person years by calendar year, sex and socioeconomic status in Sweden (Source: National Board of Health and Welfare)*

The incidence of lung cancer in Sweden is higher among residents with low socioeconomic status compared to those with middle or high socioeconomic background **(Figure 2.6.3)**, a pattern which also is present in many other countries [33 70]. The relative gap in lung cancer incidence between low and high socioeconomic groups in Sweden has increased over time, foremost among women. It has been suggested that Sweden is in the last phase of the smoking epidemic, i.e. the prevalence of smoking is declining among both men and women, and smoking has primarily become a habit of the lower socioeconomic groups [71]. In a cohort study based on information from ten European countries, adjustment for smoking explained more than 50% of the inequalities in lung cancer risk related to educational level [33].

Fatality ratio is high in lung cancer and in 2008 the ratio of mortality to incidence was 0.86 [64]. In several European countries lung cancer mortality varies between educational groups [72 73], and data suggest that differences in smoking contribute to the educational differences in overall mortality in most countries [33].

In clinical practice, lung carcinomas have divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Approximately 80% of all patients are diagnosed with NSCLC that include three major subtypes; adenocarcinomas, squamous cell carcinomas and undifferentiated large cell carcinomas. Results from a population based study in South East England suggested that adenocarcinoma was less strongly related to low socioeconomic status than other subtypes [74], which could reflect differences in smoking history. A Swedish study, found a positive association between low socioeconomic status and the risk of squamous cell

carcinoma, and concluded that the association could be mediated by smoking, life-style or occupational exposures [75].

The extent of the disease is based on tumor size (T), presence of regional lymph nodes (N) and/or distant metastases (M) according to the TNM classification [76], and further classified into clinical stages according to **Table 2.6.1.**

Table 2.6.1 *Stage at diagnosis is based on tumor size (T), presence of regional lymph nodes (N) and distant metastases (M)*

Stage at diagnosis					
M0	**T1**	**T2**	**T3**	**T4**	
N0	IA	IB	IIB	IIIB	IV
N1	IIB	IIB	IIIA	IIIB	IV
N2	IIIA	IIIA	IIIA	IIIB	IV
N3	IIIB	IIIB	IIIB	IIIB	IV
	IV	IV	IV	IV	**M1**

The literature regarding socioeconomic status and stage at diagnosis is sparse and the results are contradictory. A study on non-small cell lung cancer data observed no social differences in stage at diagnosis [77], while another population based study found evidence that deprived patients with lung cancer were more likely to present with localized disease [78]. A recent Danish study indicated that patients with low education were more likely to be diagnosed with an advanced stage at diagnosis [79].

Often, there are no clear signs and symptoms in the early stages of lung cancer and symptoms may not occur for a decade or more after the initiation of the tumor. When symptoms occur, they often indicate that the disease has progressed to an advanced stage and may include cough growth, chest pain or hemoptysis [80]. However, these symptoms, foremost cough, are also common in people free of lung cancer. An important warning sign is if symptoms change or become worse. It has been suggested that gender, health beliefs, and socioeconomic status influence how symptoms are perceived by the individual patient [81].

Because of the absence or lateness of symptoms, the majority of lung cancer patients are diagnosed with advanced disease. In 2009, only 24 percent of the patients had early stage disease (stage IA-IIB) at time of diagnosis according to the National Lung Cancer Register of Sweden [82].

Lung cancer is suspected when an abnormal spot is found on a chest X-ray. If the abnormality appears malignant, further diagnostic tests are undertaken. Diagnostic procedures and staging methods in lung cancer include chest X-ray, Computerized Tomographic (CT) scan, Magnetic resonance imaging (MRI), Positron emission tomography (PET) scan, sputum cytology, bronchoscopy, needle biopsy, thoracentesis or mediastinoscopy. Lung cancer most often metastasizes to the liver, the adrenal glands, the brain and the bones. To determine the spread of the disease, common tests include CT scan of the abdomen, CT scan of the brain and a bone scan.

Treatment depends on the type of lung cancer, anatomical location, general performance status, and the extent of the disease. Surgical resection, radiotherapy and chemotherapy are used alone or together [83]. Since small-cell lung cancer (SCLC) usually grows and spreads faster than non-small cell lung cancer (NSCLC), the treatment for SCLC is different from the treatment of NSCLC [83 84].

In early stage (stage IA-IIB at diagnosis) SCLC, the common treatment is chemotherapy and radiotherapy of the lung [84]. Due to the high risk of dissemination to the brain, it is also recommended that patients with early stage SCLC receive radiotherapy to the brain. If there is no sign of spread to the lymph nodes in the center of the chest, surgery is the choice of treatment, often followed by chemotherapy and sometimes radiotherapy [84]. However, if the disease already has spread at the time of diagnosis, surgery is not possible. In a more advanced SCLC, the common treatment is chemotherapy, but also radiotherapy or biological therapy [84].

In early stage (stage IA-IIB at diagnosis) NSCLC, the common treatment is surgery to remove part of the lung (lobectomy) or the whole lung (pneumonectomy) [83]. If surgery is not possible because of co-existing diseases or general health status, radiotherapy is the choice of treatment. Most patients are also likely to receive adjuvant chemotherapy in order to decrease the risk of recurrence. In stage III NSCLC, the most common treatment is radiotherapy, often in combination with neo-adjuvant and adjuvant chemotherapy. In stage IV NSCLC disease, treatment aims to control the cancer for as long as possible and to reduce symptoms. It has been shown that chemotherapy prolongs survival time as well as relieves symptoms in this stage, but also that radiotherapy and biological therapies can achieve symptom control [83]. All treatment modalities are associated with a variety of potentially severe and serious side effects.

The prognosis of lung cancer is in generally poor, and lung cancer remains the leading cause of cancer-related death despite some advances in treatment. Long-term survival is highly dependent on the extent of the disease at time of diagnosis and access to surgical resection. At least one study has found evidence that socioeconomic status is associated with low rate of surgery [85].

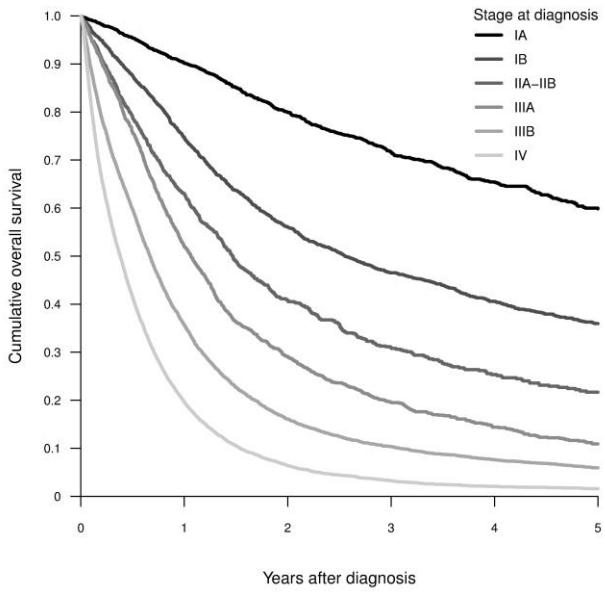

Figure 2.6.4 *Cumulative overall survival by stage at diagnosis in patients diagnosed with lung cancer between 2002 and 2009 (Source: The National Lung Cancer Register of Sweden)*

Figure 2.6.4 illustrates the cumulative overall survival by stage at diagnosis of lung cancer patients diagnosed in Sweden between 2002 and 2009. The five years overall survival in patients diagnosed with stage IA and IV at diagnosis were 60% and 3%, respectively. The majority of the patients diagnosed with lung cancer succumb to the disease, and not from competing causes. Patients with NSCLC have a better prognosis compared to those with SCLC. Other factors associated with somewhat better survival include a good general health status [86], female sex [87], and being a non-smoker [86]. Population based studies show that lung cancer survival differs between countries, e.g. with a five-year relative survival of 6.5% and 11.3% for men and 8.4% and 15.9% in women in England and Sweden, respectively [52].

Results are diverging regarding possible associations between socioeconomic status and survival, particularly since most studies to date have lacked information on clinical characteristics [88-92].

2.7 Prostate cancer

The prostate is a gland situated below the male bladder and in front of the rectum **(Figure 2.7.1)**. Almost all prostate cancers are adenocarcinomas (99%) derived from the glandular epithelial cells.

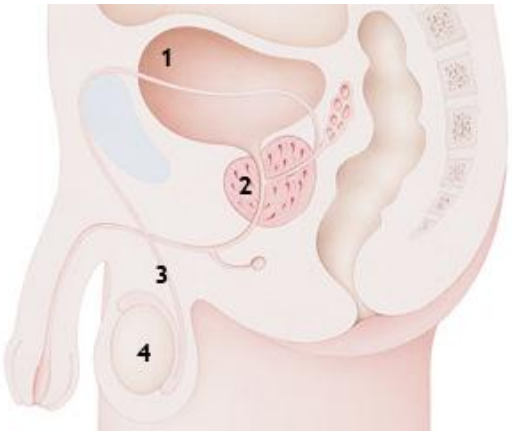

Figure 2.7.1 *Male anatomy, 1 bladder, 2 prostate, 3 vas deferens and 4 testicular (Source: Swedish Cancer Society, illustrated by Roland Klang)*

The incidence of prostate cancer has seen increased dramatically in Europe in recent decades, with an estimated 382,000 incident cases diagnosed in 2008 [20]. In Sweden, the incidence has also increased, and more than 10,000 Swedish men were diagnosed with prostate cancer in 2009 [65]. Approximately 2,500 men die from prostate cancer each year, which make prostate cancer the leading cause of cancer death in Sweden [93].

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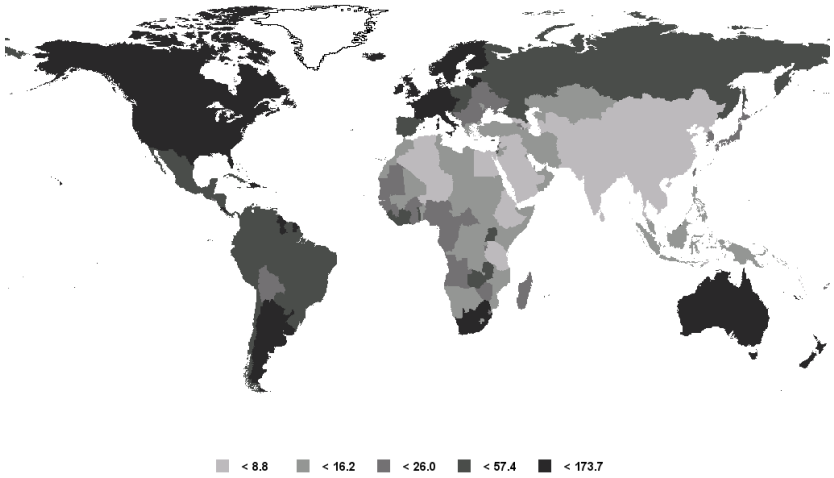

Figure 2.7.2 *Age standardized incidence rates of prostate cancer per 100,000 for men in 2008. Dark colored areas have the highest incidence rates, whereas the areas with the brightest color have the lowest incidence (Source: GLOBOCAN 2008)*

In 2008, the incidence rates of prostate cancer were higher in developed than in developing countries **(Figure 2.7.2)**. This pattern and increasing incidence trends in developing countries are likely to be explained by the introduction of the prostate specific antigen (PSA) testing amongst men with or without symptoms. Increased longevity, better disease awareness and generally improved diagnostic techniques over time may also have contributed to the observed trends.

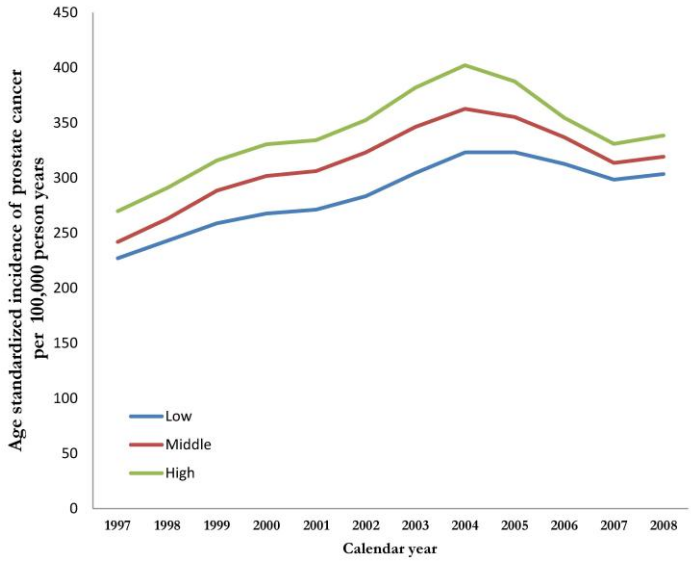

Figure 2.7.3 *Age standardized incidence of prostate cancer per 100,000 person years by calendar year and socioeconomic status in Sweden (Source: National Board of Health and Welfare)*

Swedish men with high socioeconomic status have a higher incidence of prostate cancer compared to males with a middle or low socioeconomic background **(Figure 2.7.3)**. Similar patterns have been observed in other countries [94]. The socioeconomic gradient in incidence has been relatively stable over calendar time in Sweden.

In contrast to many other malignancies, the understanding of the etiology of prostate cancer remains limited. Age represents a well-documented risk factor, but area of residence, ethnicity [95], and family history [96] also appear to play a role, while the relationship between environmental and lifestyle factors and risk remains unclear [97]. In Sweden, the median age at diagnosis decreased from 74 to 69 between 1997 and 2010, which can be attributed to a more frequent use of the PSA test [65]. There are clear geographical variations in the incidence of prostate cancer, where populations in developed countries have the highest risk **(Figure 2.7.2)**. The observed geographical variations between countries could partly be explained by differences in diagnostic intensity, but is also likely to reflect genetic and life-style factors. The incidence is higher and the mortality rate is two times higher in African-American compared to Caucasian men [98]. Results from twin studies suggest that prostate cancer has a strong heritable component, with an estimated 30 to 40 percent of the risk being explained by genetic factors [99]. The risk is higher if a brother and the father has the disease, and the younger the brother or the father was at diagnosis, the higher the risk [96]. However, recent findings from Sweden suggest an increased diagnostic activity among men with a family history of prostate cancer may explain their increased risk of prostate cancer [100]. The same study also indicated that high socioeconomic status among index patients was associated with a significant increased risk of diagnosis of prostate cancer among their brothers, especially for T1c tumors [100]. Other factors, including androgens [101] [102], diet [103], physical activity [104], sexual activity, [105] inflammation, [106] and obesity [107] have been suspected to be related to risk, but their role in prostate cancer etiology remain unclear.

Diagnostic and staging procedures in prostate cancer include digital rectum examination (DRE), prostate specific antigen (PSA) testing, trans-rectal ultrasonography (TRUS), skeletal scintigraphy, and/or the Gleason score assessed from a tissue specimen. The DRE is an examination in which the doctor palpates the prostate to search for abnormalities [108]. PSA is a glycoprotein produced by the prostate that may be found in an increased amount in the blood of men who have prostate cancer, benign prostatic hyperplasia, or infection or inflammation of the prostate [109]. The DRE and PSA exams can often detect suspicions abnormalities, but they cannot always determine whether they are due to cancer or a less serious medical condition. However, results from these tests form a basis for the physician to perform a biopsy of the gland. TRUS is a less common diagnostic procedure, where a probe is inserted in the rectum that sends out sound waves to visualize the prostate and search for abnormal areas [108].

Since the PSA test was introduced in Sweden in the 1990s, an increasing number of prostate cancer are detected in asymptomatic men. There are two ongoing screening trials that are evaluating if the PSA test should be introduced on a wider scale, one is the European Randomized Study of Screening for Prostate Cancer and the other is the Prostate, Lung, Colorectal, and Ovarian cancer screening trial [110 111]. After 15 years of follow-up, the European trial reported favorable results for the PSA test compared to patients diagnosed because of symptoms when the outcome has been overall and prostate cancer mortality [110]. However, problems with sensitivity and specificity of the test together with too short follow-up time in both trials are likely to extend the ongoing debate surrounding the PSA test for many years. An English study found that uptake clearly varies by socioeconomic status and concluded that PSA testing in general practice is currently skewed towards older men, and that current policy enabling all men to make an informed choice about PSA testing is not being effectively implemented [34]. The prevalence of urological symptoms in relation to socioeconomic status has not been described. However, one study found no association with educational status or household income after adjusting for age [112].

The introduction of the PSA test has increased the proportion of prostate cancer patients diagnosed with localized disease and, bone metastases found in screening trials have been shown to be detected at diagnosis in less than ten percent of patients. Early detection of bone metastases is critical in the management of men diagnosed with high risk prostate cancer. Skeletal scintigraphy (also referred as bone scan) has been considered the most reliable method for early detection and monitoring of bone metastases in men with prostate cancer [113].

The extent of the disease is based on tumor size (T), presence of regional lymph nodes (N) and/or distant metastases (M) according to the TNM classification [108], but also by Gleason score (the pathological grading) and the level of prostate specific antigen (PSA) **(Table 2.7.1)**.

Table 2.7.1 *Clinical risk groups based on tumor size (T), presence of regional lymph nodes (N) and distant metastases (M), Gleason score and level of prostate specific antigen (PSA)*

Clinical risk groups
1. Low risk
T1-T2, Gleason score 6 or lower and PSA < 10 ng/mL
2. Intermediate risk
T1-T2, Gleason score 7 and/or 10 ≤ PSA < 20 ng/mL
3. High risk
T3-T4 and/or Gleason score 8-10 and/or 20 ≤ PSA < 50 ng/mL
4. Regional metastases
N1 and/or 50 ≤ PSA < 100 ng/mL, no distant metastases detected (M0/MX)
5. Distant metastases
M1 and/or PSA ≥ 100 ng/mL

Treatment decisions are based on the extent of the disease, serum level of PSA, tumor size and Gleason score, but also by the condition of the host based on age, comorbidities, remaining life expectancy, and symptoms such as sexual function and anxiety. Based on these considerations, treatment pathways for prostate cancer are complex and differ greatly between doctors, hospitals, regions and countries. Treatment modalities include radical prostatectomy, radiotherapy, watchful waiting (with delayed entry of palliative care) or active surveillance (with delayed entry of curative care) and sometimes endocrine therapy [108]. Radical prostatectomy has been evaluated in both observational and randomized controlled trials, and recent trial data comparing radical prostatectomy with watchful waiting has favored radical prostatectomy in light of a significant reduction in mortality [114 115]. Results from several studies indicate that men with high socioeconomic status are more likely to receive a curative treatment [116 117]. In palliative care, numerous forms of endocrine therapies (including castration) are used alone or in combinations, but also radiotherapy and chemotherapy are used to target skeletal metastases [108].

The prognosis of prostate cancer varies greatly between countries, where a recently published population based study reported a five-year relative survival of 76.4% and 83.0% in England and Sweden, respectively [51]. Within countries survival has increased during the last decades, which may reflect a lead time bias following a more widespread use of PSA testing.

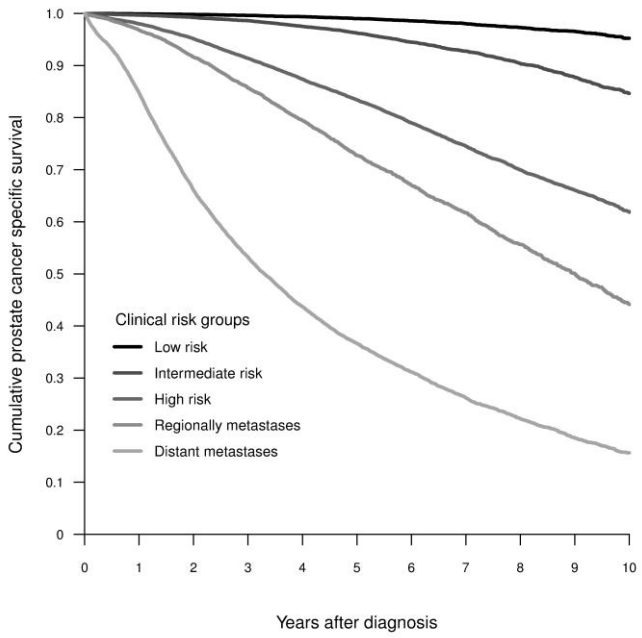

Figure 2.7.4 *Cumulative prostate cancer specific survival by clinical risk groups in men diagnosed with prostate cancer between 1997 and 2009 (Source: the National Prostate Cancer Register of Sweden)*

Figure 2.7.4 illustrates prostate cancer specific survival by clinical risk groups of men diagnosed with prostate cancer in Sweden between 1997 and 2009. The five year survival in patients with low risk and distant metastases were 99% and 38%, respectively. Social differences in survival of prostate cancer have been addressed in several studies in most of these, survival was poorer in low socioeconomic groups [118-121].

2.8 Co-existing disease among cancer patients

Older age is an important risk factor for cancer. The risk of developing cancer has been estimated to 1/10,000 per year in an individual aged 20 years, compared to 1/100 at age 80 years [122]. The presence of other medical conditions increases with age and it has been shown that cancer patients aged 70 and older have on average three comorbidities [123]. These co-existing diseases can affect the choices of management and prognosis.

Due to increased longevity and rapidly aging populations in Sweden and many other countries, the number of elderly men and women will continue to increase. A recent study has indicated that if current life expectancy trends continue, more than half of the babies born in wealthy nations today will live to be 100 years [124]. Since comorbidity burden increases with age, it will be increasingly important to consider co-existing disease in the clinical management of cancer patients. In many parts of the world the incidence and mortality of cancer is expected to have doubled by 2020 [125]. Patients with concomitant diseases may not receive optimal treatment due to preconceived notions about life expectancy and ability to tolerate therapy and side effects. There is epidemiological evidence that cancer patients with severe comorbidity receive less aggressive treatment, and that the

presence of concomitant disease affects overall and competing cause survival [123 126-128]. Some researchers have addressed comorbidity in relation to cause-specific survival with diverging results [122].

The comorbidity burden in cancer patients tends to vary by tumor sites. Approximately 85% of lung cancer patients diagnosed in Sweden are current or former smokers. Since smoking is also associated with many other medical conditions, lung cancer populations tend to have a higher comorbidity burden compared to patients with other cancer forms or to the background population. In contrast, patients diagnosed with prostate cancer, particularly those with low risk tumors, tend to be healthier than the background population in the same age.

3 AIMS

The opportunities available in Sweden for individual record-linkages between different population based registers offer unique possibilities both for epidemiological research and to examine in detail aspects of management in cancer care. The overarching aim of the present thesis was to investigate possible associations between socioeconomic status, comorbidity, management and survival in patients diagnosed with lung and prostate cancer identified in population based registers in South East England and Sweden.

Specific aims:

- **Study I:** to assess possible associations between socioeconomic status, management and survival in patients diagnosed with non-small cell lung cancer in central Sweden between 1996 and 2004.

- **Study II:** to examine possible social gradients in lung cancer survival and assess if any such variation can be attributed to social differences in comorbidity, stage at diagnosis and treatment for a setting of patients diagnosed with lung cancer in South East England between 2006 and 2008.

- **Study III:** to study aspects of management and mortality in relation to socioeconomic status in patients diagnosed with high risk prostate cancer in Sweden between 1997 and 2006.

- **Study IV:** to explore the influence of comorbidity on treatment decisions and mortality in patients diagnosed with prostate cancer in Sweden between 1997 and 2006.

4 MATERIAL

4.1 Data sources

The studies in this thesis were conducted using a population based cohort design. The Swedish studies were based on information in population based quality registers with additional data obtained by means of record-linkage to other population based health registers using the individually unique National Registration Number, assigned to all residents at time of birth or first residency. The English lung cancer study was based on information from a cancer register in South East England with additional information retrieved from hospital episodes statistics and a lung cancer audit database. The following registers were used in the present thesis:

4.1.1 The Swedish Cancer Register

Administrated by the National Board of Health and Welfare, the Swedish Cancer Register (SCR) was established in 1958 and covers the total population [58]. Reporting of all newly diagnosed tumors to the SCR is regulated by law and is mandatory for clinicians, pathologists and cytologists. The SCR includes information on selected demographic characteristics, tumor site, date of diagnosis, histological type, and stage at diagnosis (collected since 2004). Close to 99% of all cases are reported, and for 95% of the cases, the register receives two notifications. For all calendar years, the SCR translates newly reported cases back to the International Classification of Diseases-7 (ICD-7).

4.1.2 The Regional Lung Cancer Register in central Sweden

The population based Regional Lung Cancer Register (RLCR) in central Sweden (Uppsala-Örebro health care region) was established in 1995 to monitor quality of care after the introduction of regional management guidelines for lung cancer [129]. The RLCR covers >98% of all patients diagnosed with lung cancer in central Sweden, an area with a source population of 1.9 million. The RLCR contains detailed information on sex, age at diagnosis, waiting time, smoking status (current, former and non-smoker), performance status (according to the WHO classification), mode of detection, diagnostic procedures, histopathology, stage at diagnosis (according to the TNM classification) and planned initial treatment (surgery, chemotherapy, radiotherapy and no active curative treatment).

4.1.3 The Thames Cancer Register

The Thames Cancer Register is a population based cancer register (one of eleven cancer registries in the United Kingdom) and currently covers a source population of 12 million people in South East England (London, Kent, Surrey and Sussex) [130]. In total more than 2.7 million cancer cases are recorded with registration based on clinical and pathological information received from hospitals and from death certificates provided by the Office for National Statistics. The follow-up of deaths of registered cancer patients is passive, which means that all deaths (including cancer and non-cancer deaths) are notified to the Register, cancer deaths by the Office of Population Censuses and Surveys, and deaths due to other causes than cancer by the National Health Service Central Register.

4.1.4 The National Prostate Cancer Register of Sweden

A regional prostate cancer register was established in one of the six Swedish health care regions (South East) in 1987 [131]. In 1995, a urology expert group decided to develop a national clinical database for the management of prostate cancer, the National Prostate Cancer Register (NPCR) of Sweden [132] [133]. Since 1998 the NPCR covers all health care regions in Sweden. The database includes patients diagnosed with prostatic adenocarcinoma while cases detected at autopsy are not included. The NPCR is constantly updated against the Swedish Cancer Register. Currently the NPCR covers more than 98% of all patients diagnosed with prostate cancer who were registered in the Swedish Cancer Register. Through December 31, 2006, the NPCR contained data on more than 75,000 cases with detailed information on mode of detection, TNM stage, Gleason score, serum levels of prostate specific antigen (PSA) and primary treatment within six months of date of diagnosis.

The prostate cancer database Sweden (PCBaSe) is a unique database with over 75,000 incident cases with a record prostate cancer identified in the NPCR with additional data on inpatient and outpatient care, patterns of prescribed drug use and socioeconomic and familial factors obtained by means of record-linkage to other data sources [134].

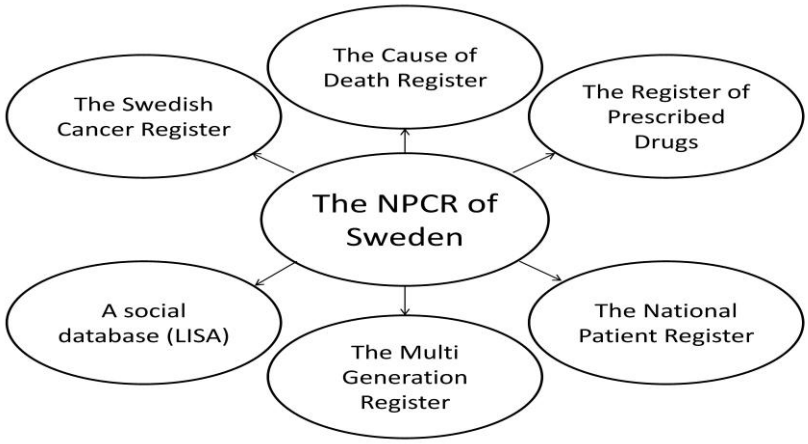

Figure 4.1.4.1 *PCBaSe Sweden; prostate cancer patients identified in the NPCR of Sweden with additional information retrieved from other population based registers in Sweden*

Figure 4.1.4.1 illustrates PCBaSe Sweden, with record-linkages between NPCR of Sweden and other population based registers in Sweden. Several topics in prostate cancer clinical epidemiology have been addressed using this database. To date, 11 studies have been published based on data from PCBaSe Sweden.

4.1.5 The National Patient Register

From 1987 the National Patient Register, administrated by the National Board of Health and Welfare, includes information on hospital admissions and discharges from all public hospitals in Sweden [135]. Each inpatient discharge record contains dates of hospital admissions and up to eight discharge diagnoses, coded according to the International Classification of Diseases.

4.1.6 The Swedish Cause of Death Register

Information on cause of death was obtained from the Cause of Death Register, administered by the National Board of Health and Welfare. The database was established in 1952 and includes records of causes of death reported by the attending physician according to WHO International Classification of Diseases. The number of non-reported deaths was estimated at 0.7% in 2006 [93].

4.1.7 Longitudinal integration database for health insurance and the labor market

The longitudinal integration database for health insurance and labor market studies (LISA) is managed by Statistics Sweden and integrates regularly updated information from the labor market, and educational and social sectors [136]. Individual level data has been collected since 1990 for all residents in Sweden aged 16 and older, and connections to family and places of employment are also available. The LISA database includes Census data, information on country of birth, year of immigration, disposable income, level of education, socioeconomic index, receipt of welfare benefits and employment status.

4.2 Study populations

Study I was based on data retrieved from the Regional Lung Cancer Register in central Sweden, with additional information obtained by means of record-linkages to the Cause of Death Register and the LISA database.

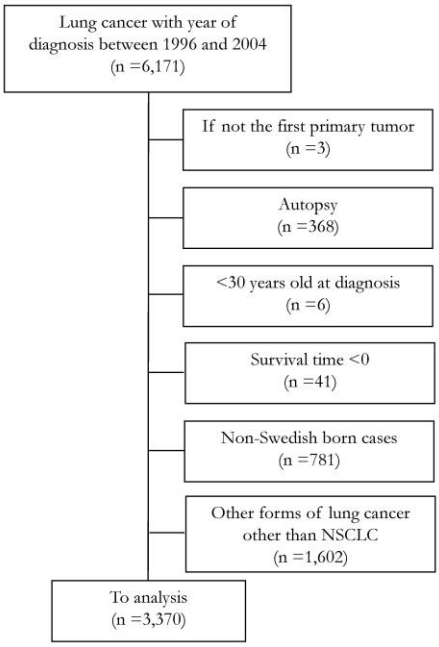

Figure 4.2.1 *Flow chart of lung cancer cohort assembly based on information in the Regional Lung Cancer Register between 1996 and 2004, and other data sources*

For the purpose of Study I, we included patients with a record of lung cancer (162 in ICD-9) diagnosed between 1996 and 2004. Lung cancers not recorded as the primary tumor and those diagnosed at autopsy or before age 30 or with negative survival time were excluded, and immigrants and patients with forms of lung cancer other than non-small cell lung cancer were also excluded (**Figure 4.2.1**). The final study population consisted of 3,370 incident cases of non-small cell lung cancer.

In study II, lung cancer cases were extracted from the Thames Cancer Register in South East England, with additional information obtained from hospital episode statistics and the National lung cancer audit database. A total of 16,183 patients were diagnosed of lung cancer between 2006 and 2008.

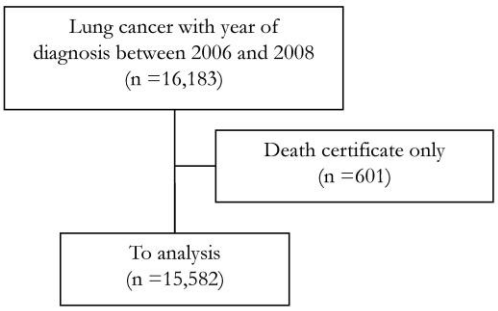

Figure 4.2.2 *Flow chart of lung cancer cohort assembly based on information in the Thames Cancer Register between 2006 and 2008*

After excluding death-certificate-only cancer registrations (601 cases or 3.7% of the total), the final study population included 15,582 lung cancer cases **(Figure 4.2.2)**.

Study III and IV were based on PCBaSe Sweden, with prostate cancer cases identified in the National Prostate Cancer Register of Sweden between 1997 and 2006.

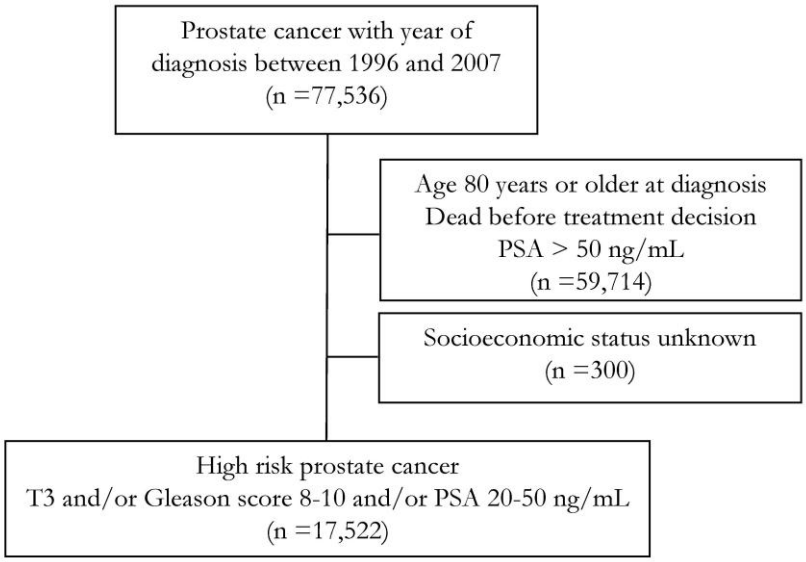

Figure 4.2.3 *Flow chart of prostate cancer cohort assembly based on information in the National Prostate Cancer Register of Sweden between 1997 and 2006, and other data sources*

In study III, the final study population was restricted to 17,522 patients diagnosed with high risk prostate cancer according the flow chart presented in **Figure 4.2.4**. In study IV, the final study population was based on all prostate cancer cases registered in between 1997 and 2006 (n=77,536).

4.3 Indicators of socioeconomic status

In the present thesis several different indicators of socioeconomic standing were included. In the first study, level of education was used as the main indicator for socioeconomic status, but associations in relation to socioeconomic index, household disposable income and number of persons in the household were also assessed. Study II utilized a deprivation index based on postcode of residence, while in study III a socioeconomic index based on occupation was used.

Educational attainment was classified into three groups according to total numbers of years of schooling: low ≤ 9 years, middle 10-12 years and high ≥ 13 years, which in the Swedish school system corresponds to mandatory school, high school or post high school education (college and university).

Socioeconomic index (SEI) was based on occupational codes from Population and Housing Census 1960, 1970, 1980, 1985 or 1990. In study I, the SEI was categorized into three levels, low (blue-collar and low level white-collar), high (intermediate and high level white-collar workers and the self-employed) and unknown (due to no employment or missing). In study III, socioeconomic index was aggregated into five levels; blue-collar workers, farmers, self-employed, lower white-collar workers and higher white-collar workers. In both the studies where patients were diagnosed after retirement, historical data were used to assess the highest lifetime SEI.

Household disposable income was divided into the lowest 50% and highest 50% income.

Number of persons in the household was categorized into one or more persons in the household.

A deprivation index was based on the income domain of the 2007 Indices of Deprivation released by the Department of Communities and Local Government [137]. The income domain is mainly influenced by different forms of social income support, in which patients are classified based on their postcode of residence and categorized into quintiles of socioeconomic deprivation, from the most affluent group to the most deprived group.

4.4 The Charlson comorbidity index

The Charlson comorbidity index (CCI) was originally proposed in 1987 by ME Charlson, to develop a simple method for classifying co-existing diseases which could predict one-year mortality using information on comorbidity from hospital chart review [138]. In that study, the derivation cohort consisted of 604 patients admitted to a New York teaching hospital during one month in 1984. The validation cohort included 685 patients diagnosed with breast cancer at a Connecticut hospital from 1962 to 1969. The final Charlson comorbidity index was the sum of 19 predefined comorbidities that were assigned weights of 1, 2, 3 or 6. These weights were based on the magnitude of the adjusted relative risks associated with each clinical condition in a Cox proportional hazards regression model **(Table 4.4.1)**.

Table 4.4.1 *Clinical conditions included in the Charlson comorbidity index (Source: Charlson ME, 1987)*

Clinical condition	Score	Clinical condition	Score
Myocardial infarct	1	Moderate or severe kidney disease	2
Congesitve heart failure	1	Diabetes	2
Peripheral vascular disease	1	Diabetes with complications	2
Dementia	1	Tumor	2
Cerebrovascular disease	1	Leukemia	2
Chronic lung disease	1	Lymphoma	2
Connective tissue disease	1	Moderate or severe liver disease	3
Ulcer	1	Metastatic disease	6
Chronic liver disease	1	AIDS	6
Hemiplegia	2		

In study II, a modified version of the Charlson comorbidity index was used with the approach that all weights except cancer were included to assess the burden of concomitant disease for each patient, following retrieval of information on comorbidity from the hospital episode statistics in a three-year period preceding the lung cancer diagnosis. In a subsequent step, the weights were summed to obtain an overall score, resulting in three comorbidity levels; no (0), mild (1), and severe comorbidity (2+). A total of 1,808 (11.6%) lung cancer patients had no information available on comorbidity since no link to the hospital episode statistics could be established.

In study III and IV, information on medical conditions other than cancer was obtained from the Swedish National Patient Register, where the main diagnosis and up to seven secondary discharge diagnoses from in-hospital stays preceding the prostate cancer diagnosis were retrieved. Malignancies other than prostate cancer were identified in the Swedish Cancer Register. All information on concomitant disease was retrieved from ten years before, up until the date of the prostate cancer diagnosis. The CCI was then used to assess the burden of concomitant disease for each patient with prostate cancer. All 19 weights in **Table 4.4.1** were summed to obtain an overall score for all patients, and that resulted in the three comorbidity levels of CCI 0 for no comorbidity, CCI 1 for mild and CCI 2+ for severe comorbidity.

5 STATISTICAL METHODS

In all four studies, descriptive statistics were calculated using conventional methods. An overview of the statistical methods used is presented in **Table 5.1**. All p-values were two-sided and statistical significance was considered at $p<0.05$. Data management was carried out using SAS 9.1/9.2, while statistical analyses and graphical illustrations were performed using R 9.2 and/or STATA 11.

Table 5.1 *An overview of the statistical methods used*

Statistical methods	Study			
	I	II	III	IV
Binary logistic regression	X	X	X	X
Time to event analysis				
Kaplan-Meier	X			X
Cox regression	X	X	X	X
Cumulative incidence function			X	X
Conditional probability function				X
Fine and Gray's competing risk regression			X	X
Flexible parametric models		X		
Multiple imputation for missing data		X		

5.1 Binary logistic regression

Binary logistic regression is used in epidemiological research to predict the probability of occurrence of an event (treatment or no treatment) by fitting data as a function of one or several dependent variables, allowing for management of potential confounders. An odds ratio is a natural description of an effect in a probability model and in the studies included, estimated odds ratios with 95% confidence intervals are used as a measure of effect. Events of interest were stage at diagnosis (study II) and different treatment modalities (all studies) and the exposure variables were socioeconomic status and comorbidity burden both univariate and adjusted for potential confounders. The goodness of fit of the models was evaluated by using the model deviance and likelihood ratio tests were used to assess the relative importance of the model covariates.

5.2 Time to event analysis

In time to event analysis there are three key parts that should be considered: events, failure time and censoring time. The event is defined as the outcome of interest, e.g. lung cancer death or prostate cancer death. The date of the occurrence of the event must also be known. The time from the baseline (in the present studies, date of cancer diagnosis) to the occurrence of the event (the failure) is referred to as the failure time. When an event is not observed before end of follow-up, the failure time is referred as right censored (e.g. the patient

emigrated during follow-up or is lost from the study for some other reason before the event of interest is observed) and the follow-up is defined as censoring time (instead of failure time). In the present studies, survival time was defined as the interval between the date of the primary diagnosis of lung or prostate cancer and either the date of the event (death due to all causes, lung cancer, prostate cancer, and causes other than prostate cancer) or emigration or end of follow-up. In study I and II, end of follow-up was on 31 December 2006 and on 31 December 2009, respectively. In Study III and IV, end of follow-up was on 31 December 2007.

5.2.1 The Kaplan-Meier estimator

The Kaplan-Meier approach [139], also known as the product limit estimator, was used to measure the fraction of patients living for a certain time post cancer diagnosis for each variable of interest. The Kaplan-Meier estimation leads to a life table with the smallest possible intervals which use the maximum amount of information in the data. Although the probability calculated at any given interval is not very accurate because of the small number of events, the overall probability of surviving to each point (e.g. three-year survival) is more accurate. The Kaplan-Meier approach was used to evaluate the cumulative survival (cause-specific and overall) comparisons between socioeconomic groups and also in relation to comorbidity burden.

5.2.2 Cox Proportional Hazard regression

The Cox proportional hazard regression is widely used in time to event analysis [140]. The Cox model is a semi-parametric model where the baseline hazard function does not have to be specified, but where parametric assumptions about the effects of covariates of the hazard function do have to be made. Thus, we assume that any two or more hazard rates predicted by the model are proportional over time. The Cox model was used in all studies, where relative risks were expressed as hazard ratios with 95% confidence intervals. This measure how much a covariate increases or decreases the rate of the event of interest, assuming that it acts multiplicatively. In the lung cancer studies, both cause-specific and overall deaths were considered as an event, with educational level and deprivation index as exposure variables. These models were adjusted for demographic, clinical and treatment factors. In the prostate cancer studies, overall death was used as an event using the Cox model. The exposure variables were comorbidity burden and socioeconomic status adjusted for demographic and clinical characteristics. In all models, the Schoenfeld's residuals were plotted against survival time and tested to verify that assumptions of proportional hazards were fulfilled.

In study II we calculated the relative contribution (%) of adding each covariate separately in explaining the possible social variation in mortality between the most deprived (SES_{Q5}) and the most affluent (SES_{Q1}) patients as follows:

$$\left(\frac{\boldsymbol{HR\ for\ SES_{Q5}\ in\ Model\ A - HR\ for\ SES_{Q5}\ in\ Model\ B}}{\boldsymbol{HR\ for\ SES_{Q5}\ in\ model\ A - 1}}\right) \times \mathbf{100}$$

Where Model A is the basic model (socioeconomic quintiles and adjusted for sex) and in Model B, each covariate is added to Model A.

5.2.3 Competing risks

In the Kaplan-Meier approach, and in the Cox model we considered situations where each patient could only have one event (all other events were censored). However, there are situations where it may not be appropriate to apply the usual survival methods to the time to event analysis [141]. One such situation is where competing risks are present [142]. A competing risk arises when a patient can experience more than one type of event and the occurrence of one type of event hinders the occurrence of other types of events, e.g. men diagnosed with prostate cancer may die of other causes than prostate cancer. This is a competing risk situation because death from other causes prohibits the occurrence of prostate cancer death. Prostate cancer death is considered the event of interest, while death from other causes is considered a competing risk. The group of patients that died from other causes cannot be considered censored, since their observations are not incomplete. Since most lung cancer patients succumb to their disease, competing risks analysis was only considered in the prostate cancer studies (Study III and IV).

5.2.4 Cumulative incidence function

Given that the Kaplan-Meier estimator ignores events of all types other the one of interest, it can be interpreted as the probability of an event beyond a specific time given that all other risks are removed. However, this may be a nonsensical interpretation in many medical situations, e.g. if the event of interest is relapse of prostate cancer in the presence of the competing risk of death due to non-relapse-related causes, then one would be forced to consider the unrealistic case where death due to all non-relapse-related causes was eliminated. To estimate the probability of an event in a competing risk situation, Kalbfleisch and Prentice suggested the cumulative incidence function [143]. The definition of cumulative incidence function states that the cumulative incidence is a function of the hazards of all the competing events and not solely of the hazard of the event to which it refers. The sum of the cumulative incidence function has the nice feature that it equals the complement of the overall Kaplan-Meier estimate of survival considering failures of any kind. In the third and fourth study, the cumulative incidence function was used to estimate the cumulative incidence of death due to prostate cancer when death due to other causes also was considered. The cumulative incidence functions were stratified on comorbidity and socioeconomic status and expressed as the cumulative probability of mortality since diagnosis.

5.2.5 Fine and Gray's Competing risk regression

When competing events are present, the focus will be on the cumulative incidence function rather than the survival function. Modeling in the presence of competing risk can be applied using the Cox model with competing risks, but either the interpretations have to be modified or a lot of work has to be done to assess covariate effects. In 1999, Fine and Gray suggested competing risks regression as a useful alternative [144]. The Fine and Gray's competing risk regression was used in the prostate cancer studies, with both deaths due to prostate cancer and to other causes as the primary events of interest, where the estimates were expressed as subdistribution hazard ratios with 95% confidence intervals.

5.2.6 Conditional probability function

Previous studies have indicated that the cumulative incidence function for the event of interest may not include a complete understanding of competing risks data. The reason behind this indication is that the cumulative incidence function for the event of interest may appear low only because the cumulative incidence function for the competing risk is large. Calculating the conditional probability is one way to incorporate the two types of information; the event of interest and the competing risk [145]. The conditional probability is calculated as the probability of observing an event of interest, conditional on the patient not experiencing a competing risk event. In study IV, we calculated conditional probabilities by comorbidity burden since most of prostate cancer patients with severe comorbidity do not die from their disease, and that death rate from competing causes increased with comorbidity burden, expressed as the conditional prostate cancer mortality since diagnosis.

5.2.7 Flexible parametric models

In study II, we estimated the cumulative survival and mortality rates, calculated as number of deaths divided by person-years at risk. These estimates were modeled through flexible parametric survival models using a restricted cubic spline for the baseline mortality rate. These models, similar to the Cox models, provide hazard ratios with 95% confidence intervals as a measure of association between exposures and outcome. By modeling the underlying rate parametrically, it is possible to estimate various fitted curves from the model, such as the cumulative survival. In the Cox models, we estimated a constant hazard ratio between the exposure variable throughout follow-up. In the flexible parametric survival framework, the hazard ratio for the exposure variable of interest was estimated as a function of follow-up using a second spline function. The hazard ratio is then time-dependent due to the underlying timescale of time since diagnosis of lung cancer. All flexible parametric survival models were estimated using the stpm2-package [146].

5.3 Multiple imputation

In study II, we used multiple imputation which is a simulation based approach for analyzing incomplete data. Multiple imputation replaces missing values with multiple sets of simulated values to complete the data, applies standard analyses to each completed dataset, and adjusts the obtained parameter estimates for missing data uncertainty. Multiple imputation handles missing data in such a way that a valid statistical inference can be obtained. Since more than ten percent of the patients in study II had no information on comorbidity burden, the multiple imputation method was applied with information based on their sex, histology and treatment factors using chained equations with 60 imputated datasets [147].

6 SUMMARY OF STUDIES

6.1 Study I: Social inequalities in non-small cell lung cancer management and survival - A population based study in central Sweden

Introduction

The prognosis of lung cancer is generally poor, with long-term survival depending on early diagnosis and surgical resection. Several investigators have shown that men and women with low socioeconomic status have an increased risk of developing lung cancer, but few studies have examined possible socioeconomic inequalities in access to treatment and in survival. The aim of the present study was to examine possible associations between socioeconomic status, management and survival in patients diagnosed with non-small cell lung cancer (NSCLC).

Material and Methods

In this population based cohort study, 3,370 patients diagnosed with NSCLC between 1996 and 2004 were identified in the Regional Lung Cancer Register in central Sweden, with record-linkages to the Cause of Death Register and a social database (LISA). While several indicators of socioeconomic standing were used, level of education was chosen as the main indicator for socioeconomic status, and was categorized in three levels: low, middle and high education. Binary logistic regression with odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess associations between educational level and care management, while Kaplan-Meier estimates and the Cox regression model were used with hazard ratios (HRs) to examine associations between educational level and survival.

Results

NSCLC patients with low education were older at diagnosis, were more often smokers, and had a lower performance status compared to patients with high education. There were no clear differences by level of education with regard to stage at diagnosis. However, a greater diagnostic intensity was observed in patients with high education. A difference in time from referral to diagnosis by level of education was observed, foremost in early stage disease, where the median waiting time for the low and high education groups was 32 and 17 days, respectively.

In early stage disease, following adjustment for demographic and clinical characteristics, the likelihood to undergo surgery was higher in patients with high education (OR 2.84; 95% CI 1.40 to 5.79). Differences in receiving radiotherapy or chemotherapy were most pronounced in stage III disease at diagnosis, where 33.8% and 40.6% of patients in the low education group compared to 42.5% and 60.5% in the high educational group received radiotherapy or chemotherapy, respectively.

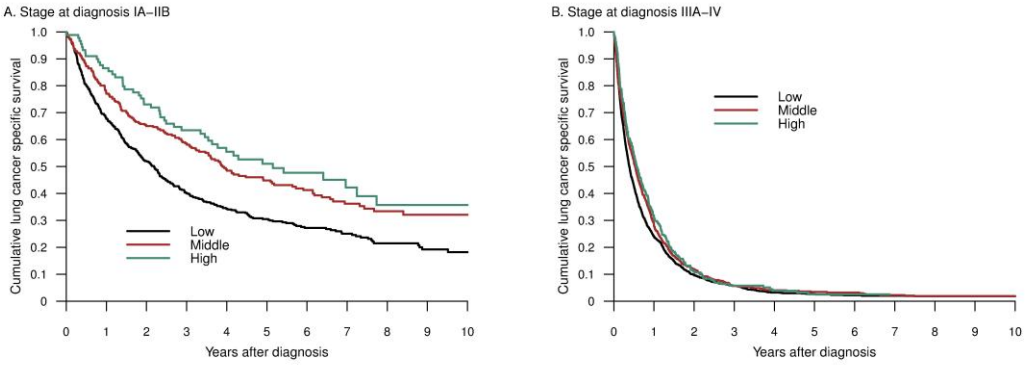

Figure 6.1.1 *Cause specific cumulative survival by stage at diagnosis and level of education*

A social difference was observed in survival for all socioeconomic indicators, except for the indicator number of people in the household. The social variation in survival was most pronounced in early stage disease, where the three-year survival in low and high education patients was 39% and 65%, respectively **(Figure 6.1.1)**. In a model adjusted for demographic and clinical characteristics, the risk of death was lower among patients with high compared to low education, but only in early stage disease (HR 0.58; CI 95% 0.40 to 0.85). In a multivariate model, when also including treatment, a lower risk of death was observed among high educational patients, but only among women in early stage disease (HR 0.33; CI 95% 0.14 to 0.77).

Conclusion

The present results indicate that disadvantaged patients receive less intensive care for non-small cell lung cancer within the setting of the Swedish National health care system. Of particular concern was our finding of disparities in the likelihood to undergo surgery in early stage disease, a treatment of significant potential benefit. The pattern of care and survival observed in the most privileged groups should represent a minimum standard for all patients with lung cancer.

6.2 Study II: Social differences in lung cancer management and survival in South East England – The role of patient, clinical and treatment factors

Introduction

Recent studies in the United Kingdom have found evidence of both regional variations in treatment intensity and socioeconomic differences in lung cancer survival. The aim of the present study was to examine possible social variations in lung cancer survival and assess if any such gradients can be attributed to social differences in comorbidity, stage at diagnosis or choice of treatment.

Material and Methods

In this population based cohort study, 15,582 patients in the Thames Cancer Register in South East England were diagnosed with lung cancer between 2006 and 2008. Socioeconomic status was based on the income domain of the 2007 Indices of Deprivation (socioeconomic quintiles). Logistic regression with odds ratios was used to assess associations between socioeconomic quintiles, stage at diagnosis and choice of treatment. Flexible parametric models and Cox regression with hazard ratios were used to assess associations between socioeconomic quintiles and overall survival.

Results

The likelihood of being diagnosed with early stage disease did not vary by socioeconomic quintiles (p=0.58). In early stage NSCLC, and following adjustment for sex, age and comorbidity, the likelihood to undergo surgical resection was lowest in the most deprived group, but there was no clear trend through all socioeconomic quintiles (p=0.29). In stage III disease, there were no socioeconomic differences in the likelihood to receive radiotherapy, while in advanced disease or SCLC, receipt of chemotherapy differed over socioeconomic quintiles (p<0.01).

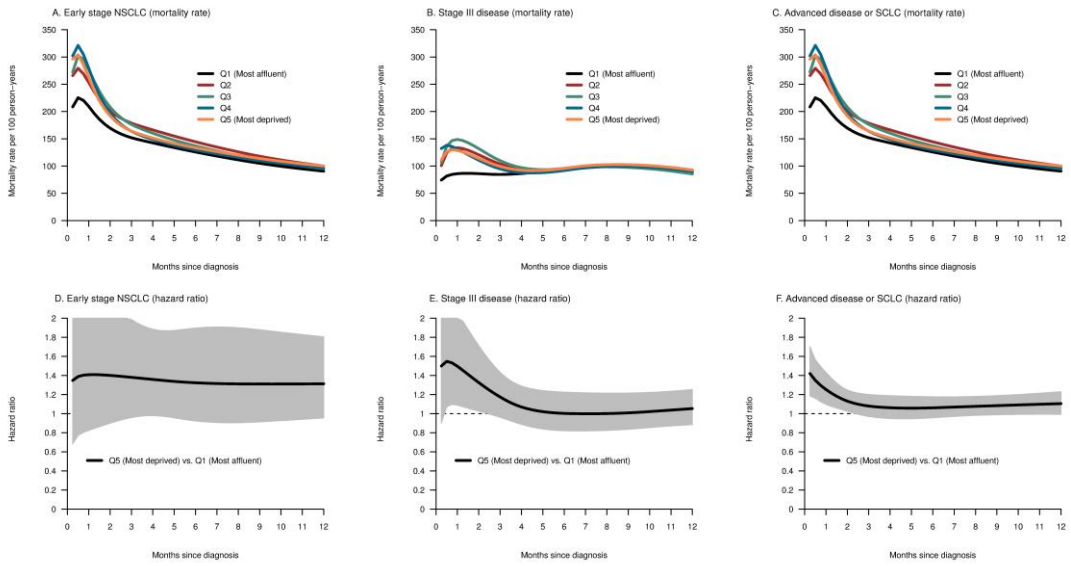

Figure 6.2.1 *Estimated mortality rates by socioeconomic quintiles and time-dependent hazard ratios between the most deprived versus the most affluent patients within 12 months of diagnosis by tumor subgroups*

In early stage disease and following adjustment for confounders, the hazard ratio between the most deprived and the most affluent group was 1.24 (95% CI 0.98 to 1.56). Corresponding estimates in stage III and advanced disease or small cell lung cancer were 1.16 (95% CI 1.01 to 1.34) and 1.12 (95% CI 1.05 to 1.20), respectively.

Figure 6.2.1 illustrates the estimated mortality rates by socioeconomic quintiles and crude time-dependent hazard ratios between the most deprived versus the most affluent patients within 12 months of diagnosis by tumor subgroups. In early stage disease, the hazard ratio between the most deprived and the most affluent group was approximately 1.4 and constant through follow-up, while in patients with advanced disease or small cell lung cancer no difference was detectable after three months.

Conclusion

We observed social variations in management, but also in survival in patients diagnosed with lung cancer in South East England between 2006 and 2008. These inequalities could not be fully explained by social differences in stage at diagnosis, comorbidity and treatment. The survival observed in the most affluent patients should set the goal for what is achievable for all lung cancer patients managed within the same health care system.

6.3 Study III: Differences according to socioeconomic status in the management and mortality in men with high risk prostate cancer

Introduction

In recent studies, we have found evidence of social inequalities in the management and survival of patients diagnosed with lung, colorectal and breast cancer in Sweden. Over the past two decades, the incidence of prostate cancer has increased rapidly in most Western countries with reports of a higher incidence in high compared to low socioeconomic groups. The present study aimed to investigate possible associations between socioeconomic status, metastatic work-up, treatment and mortality in patients diagnosed with high risk prostate cancer in Sweden.

Material and Methods

In this population based cohort study, we used data from a comprehensive database (PCBaSe Sweden) including prostate cancer patients identified in the NPCR of Sweden between 1997 and 2006 with additional information retrieved from other population based registers. High risk prostate cancer was defined as clinical T3 tumor, and/or Gleason Score 8–10 and/or prostate specific antigen levels of 20–50 ng/mL. Logistic regression with odds ratios (OR), Cox regression with hazard ratios (HR), and Fine and Gray's competing risk regression with subdistribution hazard ratios (sHR) were used to assess associations between socioeconomic status, bone scan, intention to treat, curative treatment, and mortality adjusted for comorbidity, age, calendar period and clinical subgroups. Socioeconomic status was based on occupation and categorized into five levels; blue-collar workers, farmers, self-employed, lower white-collar workers and higher white-collar workers.

Results

A total of 17,522 patients diagnosed with high risk prostate cancer between 1997 and 2006. Of these, 6,681 (38.1%) were blue-collar workers. Patients registered as blue-collar workers were older at diagnosis and had a higher comorbidity burden compared to higher white-collar patients. **Figure 6.3.1 a)** illustrates the likelihood to undergo a bone scan by socioeconomic status, adjusted for calendar period, age at diagnosis, clinical subgroups and comorbidity. A bone scan was significantly more likely to be performed in higher white-collar workers compared to blue-collar workers (OR 1.30; 95% CI 1.21 to 1.40).

Among patients with high risk prostate cancer free from metastases based on the results from the bone scan, differences in intention to treat between higher white-collar and blue-collar workers remained after adjustment for potential confounders (OR 1.43; 95% CI 1.28 to 1.57) **(Figure 6.3.1 b)**.

A total of 4,304 (47.9%) men free of metastases underwent curative treatment. In men with higher white-collar background, 34.5% underwent radical prostatectomy compared to 28.3% of blue-collar worker patients. Following adjustment for demographic and clinical characteristics, patients from the higher white-collar group were more likely to undergo radical prostatectomy compared to blue-collar patients (OR 1.29; CI 95% 1.10 to 1.47) (**Figure 6.3.1 c)**.

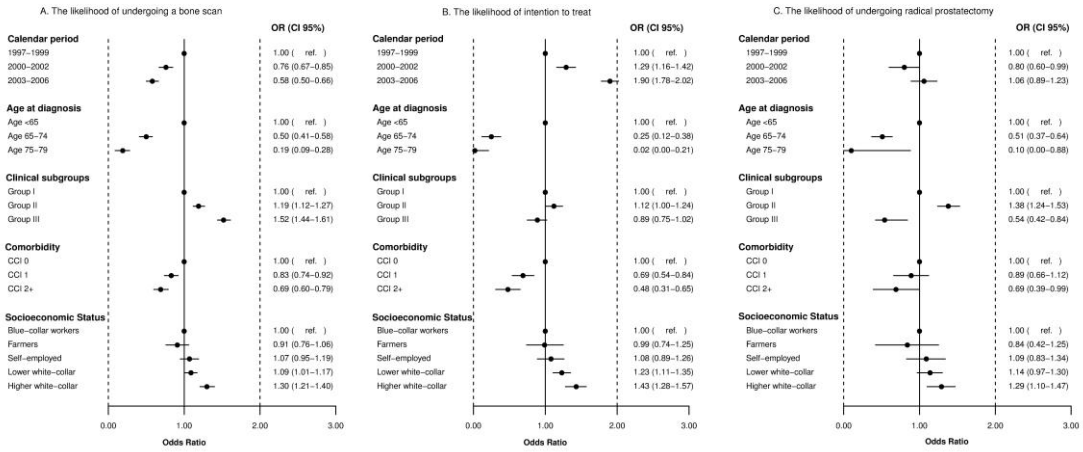

Figure 6.3.1 *Likelihood of a) bone scan, b) intention to treat, and c) radical prostatectomy in patients diagnosed with high risk prostate cancer*

In men that underwent curative treatment following a bone scan, the cumulative probability of prostate cancer death was 10.0% (95% CI 6.7 to 13.3%) amongst higher white-collar workers and 14.4% (95% CI 11.2 to 17.8%) in blue-collar workers **(Figure 6.3.2)**. In the same treatment subgroup of patients, a social gradient in both overall and cause-specific mortality persisted after adjustment for potential confounders (higher white-collar versus blue-collar workers; overall HR 0.76; CI 95% 0.60 to 0.97, cause-specific sHR 0.70; CI 95% 0.49 to 0.99).

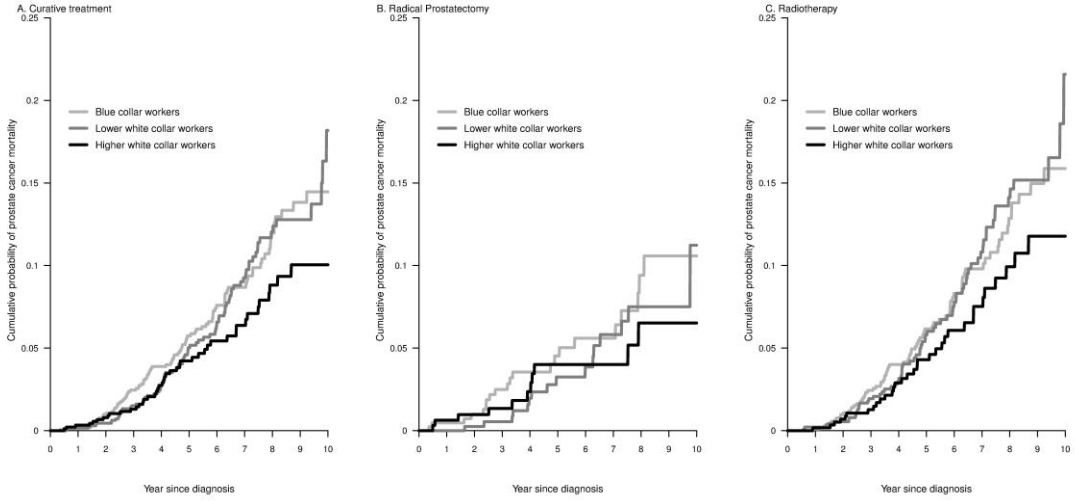

Figure 6.3.2 *Cumulative probability of prostate cancer death by socioeconomic status in patients diagnosed with high risk prostate cancer free from metastases that underwent curative treatment*

Conclusion

We conclude that socioeconomic disparities in management and mortality in men with high risk prostate cancer exist also within the setting of a National health care system aiming to provide care on equal terms to all residents.

6.4 Study IV: Comorbidity, treatment and mortality – A population based cohort study of prostate cancer in PCBaSe Sweden

Introduction

Increased longevity will lead to aging populations and a higher prevalence of men with prostate cancer. Since the comorbidity burden increases with age, it will be increasingly important to consider co-existing disease in the clinical management of cancer. We aimed to examine in detail the influence of comorbidity on treatment decisions and mortality using a competing risk approach in men diagnosed with prostate cancer.

Material and Methods

For the purpose of the present study, we used information available in PCBaSe Sweden, a prostate cancer database of men diagnosed with prostate cancer identified in the National Prostate Cancer Register of Sweden, with record-linkages to the Swedish Cancer Register, the National Patient Register and the Cause of Death Register. The Charlson comorbidity index (CCI) was used to assess the burden of co-existing disease for each patient, categorized into three comorbidity levels; CCI 0 for no comorbidity, CCI 1 for mild and CCI 2+ for severe comorbidity. Binary logistic regression was used to assess associations among CCI and treatment modalities with odds ratios (OR) and 95% confidence intervals (CI). Cumulative and conditional incidence functions were derived to assess associations between CCI and mortality, while the Cox regression with hazard ratios (HR) and the Fine and Gray's competing risk regression with subdistribution hazard ratios (sHR) were used to adjust for demographic and clinical characteristics.

Results

A total of 77,536 men were diagnosed with prostate cancer between 1997 and 2006. Of these, 21,915 (28.3%) patients had at least one other medical condition, recorded in the National Patient Register. Prostate cancer patients with no record of comorbidity were younger at diagnosis, and were more often detected by a health control (28.3%) compared to patients with severe comorbidity (12.1%). 13,428 (25.3%) men without comorbidity had low risk prostate cancer compared to 1,792 (14.7%) men with severe comorbidity.

Among patients diagnosed with low risk prostate cancer, 5,975 of the 13,245 (45.1%) with no record of comorbidity underwent radical prostatectomy compared to 1,399 (18.3%) with severe comorbidity. In the same clinical risk group, the distribution for surveillance as the primary choice of management between patients without and with severe comorbidity was 38.9% and 63.3%, respectively. Following adjustment for age and calendar period of diagnosis, patients with severe comorbidity were less likely to undergo radical prostatectomy (OR 0.51; 95% CI 0.43 to 0.60), while the likelihood of surveillance was significantly higher in patients with severe comorbidity (OR 1.50; 95% CI 1.32 to 1.70).

In patients diagnosed with high risk prostate cancer, gonadotropin-releasing hormone analogues (GnRH) were the most common mode of treatment independent of comorbidity burden. In the same clinical subgroup, radiotherapy was more common (range 7.7% to 21.3%) than radical prostatectomy (range 3.0% to11.2%) regardless of comorbidity burden. Following adjustment for age and calendar period, patients with severe comorbidity were

less likely to receive radiotherapy or to undergo radical prostatectomy compared to those with no concomitant disease (radiotherapy, OR 0.57; 95% CI 0.49 to 0.66; radical prostatectomy, OR 0.51; 95% CI 0.41 to 0.65). In high risk prostate cancer, or distant disease, patients with severe comorbidity were less likely to be treated with anti-androgens compared to patients with no record of comorbidity. Patients in all clinical subgroups with severe comorbidity were more likely to receive GnRH compared to men free of comorbidity ($p<0.01$), with the exception of patients with distant metastases.

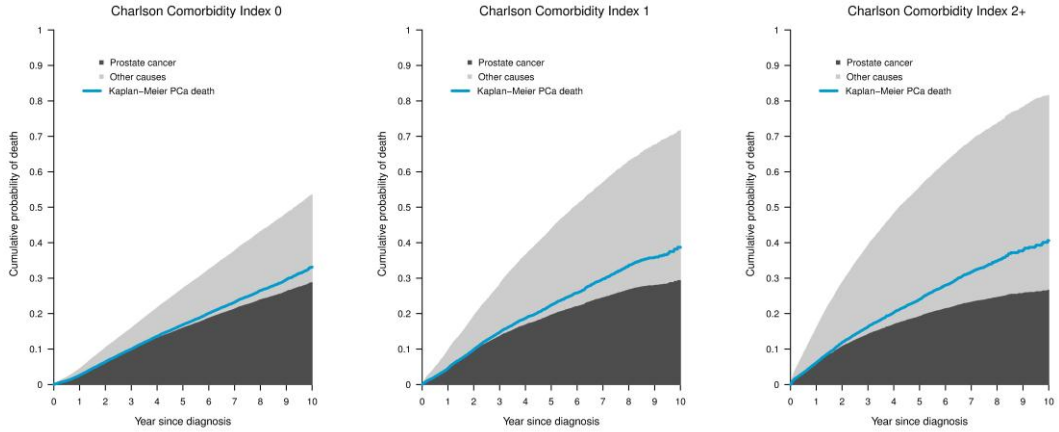

Figure 6.4.1 *Cumulative probability of death by Charlson comorbidity index*

Figure 6.4.1 shows the cumulative probability of mortality by comorbidity burden using three different endpoints. When considering mortality from competing causes, the probability of prostate cancer mortality was lower in men with severe comorbidity compared to those with no registered concomitant disease, but was higher for mortality from other causes. In the Kaplan-Meier estimates of prostate cancer mortality, the estimate was consistently higher in patients with severe comorbidity.

Using the Cox model and Fine and Gray's competing risk regression, and following adjustment for age at diagnosis, calendar period, and clinical risk group, patients with severe comorbidity had a higher all-cause and competing cause mortality, but not prostate cancer specific mortality (all-cause HR 1.99; 95% CI 1.93 to 2.05; competing cause sHR 2.66; 95% CI 2.56 to 2.78; prostate cancer specific sHR 0.98; 95% CI 0.93 to 1.03). In patients with low risk prostate cancer and severe comorbidity, the risk of competing cause mortality was more than threefold higher in patients with severe comorbidity compared to men without comorbidity (sHR 3.39; 95% CI 3.00 to 3.84). Prostate cancer specific mortality was not elevated in any clinical risk group among patients with severe comorbidity.

Figure 6.4.2 illustrates the cumulative probability of prostate cancer death, given no death from competing causes, by clinical risk group and comorbidity burden. In all clinical risk groups, the conditional prostate cancer death was higher in patients with severe comorbidity in contrast to patients with no record of coexisting disease ($p<0.01$). The difference in conditional prostate cancer mortality by comorbidity burden increased throughout follow-up, except in distant metastatic disease.

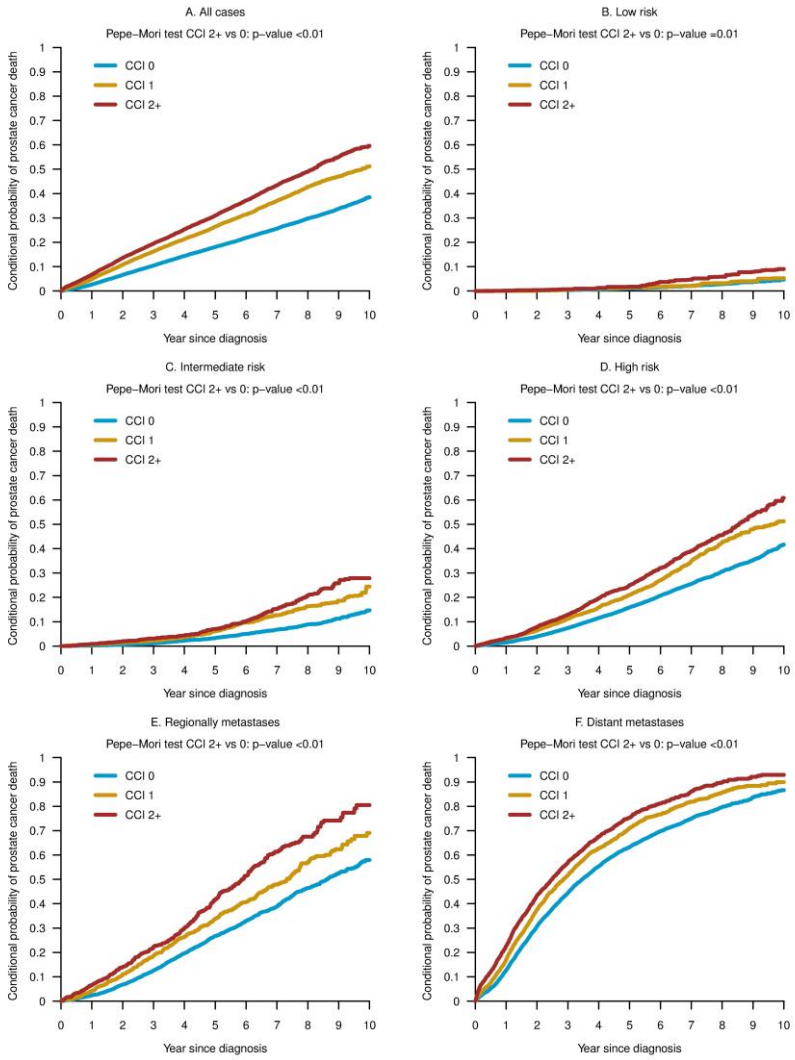

Figure 6.4.2 *Cumulative probability of prostate cancer mortality, given no death due to other causes, by clinical risk groups, treatment modalities and comorbidity burden*

Conclusion

The present findings indicate that the presence of concomitant disease is considered in the treatment decisions for patients with prostate cancer. Patients with severe comorbidity received curative treatment less often, and had a higher all-cause and competing cause mortality, but lower prostate cancer specific mortality. However, in conditional probability prostate cancer mortality analyses given no death from other causes, men with severe comorbidity had a higher prostate cancer specific mortality.

7 DISCUSSION

7.1 Methodological considerations

In general the findings reported in this thesis were in line with results from most previous studies in this area. There was also a consistency in findings with regard to the role of socioeconomic factors between our different studies. However, all observational studies are more or less prone to errors. Two main types of error are present in epidemiological studies: systematic and random errors. Bias is another term for systematic error. A study can be biased because of the way the subjects have been selected, the way the study variables have been measured or confounding factors. The validity of an observational study depends on the degree of systematic error, and the concept of validity is usually discussed in terms of internal and external validity. Random errors result from the play of chance and are related to the concept of precision. The precision of a result is decided by the level of random errors. Random errors would be reduced to zero if a study becomes infinitely large.

7.1.1 Internal validity

A strong internal validity means measurements of the exposure and the outcome variables are reliable, and in studies of causation, a strong internal validity justifies the causally links between the exposure and outcome variables [148]. There are three broad categories of threats to internal validity that must be considered: selection bias, information bias and confounding, which once introduced into a study are difficult to remove.

Selection bias is a systematic error that in retrospective cohort studies may occur if the risk of outcome influences the probability of being included in the exposed (or unexposed) group, or influences the way in which exposure is defined [148]. In the present studies, virtually all lung and prostate cancer cases in the regions under study were included. In Sweden, the completeness of the quality registers for lung cancer in central Sweden, and prostate cancer in Sweden exceed 95% in comparison to cases registered in the Swedish Cancer Register. However, a small proportion of all cancers remain undetected during life or are not registered in the Swedish Cancer Register, especially for cancer sites with poor prognosis such as lung cancer [58], and that are detected for the first time at autopsy. Lung cancer cases detected at autopsy were only registered in the first calendar period in the Regional Lung Cancer Register (1995-2000), and autopsy cases are not included in the National Prostate Cancer Register of Sweden. Furthermore, it cannot be ruled out that socioeconomic status might affect the probability that a malignancy remains undetected until after death.

Information bias occurs when information on exposures and outcomes are erroneous [148]. In all our studies exposure information was retrieved from population based registers of high quality, which reduced the risk of misclassification. Differential misclassification of exposure occurs if the misclassification is dependent on the outcome, or non-differential if it is unrelated to the outcome. Differential misclassification is problematic and can either

exaggerate or underestimate an effect, whereas non-differential misclassification tends to bias an association towards the null or no-effect value.

The different indicators of socioeconomic status used as exposures in the present thesis have different properties and limitations. In study I, level of education was used as the main indicator of socioeconomic status. Level of education has the advantage of being relatively easy to measure, it is generally uncontroversial (as opposed to other measurements of socioeconomic status such as income), it can capture socioeconomic status in the early stages of a subjects life, it is broadly stable throughout the course of life and usually predates and to some degree determines employment and the ability to earn income [149 150]. Level of education has also been shown to be a good indicator of social position in relation to health and survival [151], particularly since it may also reflect dimensions of health awareness and ability to access and navigate the health care system [152]. A disadvantage of education is that it is generally fixed in adult life and for some countries it shows little variation. Also, it can be affected by birth cohort effects in that educational systems change over time. Also, education level is not always readily transferable between countries, cultures and educational systems and it only provides information on quantity rather than educational quality [149 150].

In study II, based in South East England, an area-based measurement of deprivation was used. The income domain of the Indices of Deprivation has been found to perform better than earlier area-based measurements used in the United Kingdom [153]. One of the key criticisms of the present indices has been the inclusion of health domain and the concern of mathematical coupling, the phenomenon whereby two variables will inevitable correlate if they share elements of each other. In study II, the area-based measurements were used as indicators for the deprivation of individual lung cancer patients at the time of diagnosis, an approach that is likely to lead to an underestimation of social differences in survival [154]. In addition, the variability in socioeconomic status based on area characteristics will always be smaller than that of the individual factor, that is, the lowest value in the area income will always be higher than the lowest individual income, and vice versa for the highest income [155].

In study III, occupation which has the advantage of being widely available in routine Census data, was used as an indicator for socioeconomic status. Occupation represents a major link between education and income, such that education determines occupation which in turn is related to income. Furthermore, occupation is not only a major influential factor on the stratification of society, but it is also a major influence on the structure of an individual's life [149 150 156]. However, the method of coding occupations to different social classes is arbitrary and somewhat subjective where each stratum can be heterogeneous in terms of education and income. Furthermore, a significant proportion of the population will not be assigned socioeconomic status (including unemployed, retired people, students), and occupational classifications also struggle to keep up with continually evolving and more complex jobs. In study I and III, historical data were used to assess the highest lifetime socioeconomic status in patients diagnosed after retirement.

In study IV, we used the Charlson comorbidity index (CCI) as the exposure variable and an indicator for comorbidity burden, while it was used as a covariate in study II and III. The CCI has been validated in several studies [157-159], but it does not, however, permit

distinguishment between the mildest and the most severe cases in each category of comorbidity burden, since the index is based on discharge diagnosis from inpatient admissions only. Furthermore, patients who were treated for their medical condition solely by their general physician score 0 in the index, which could lead to an underestimation of comorbidity burden when using only the CCI as an exposure variable.

In study II, where treatment was used as an outcome, it was based on registration of 'Yes' or 'Unknown'. However, it was unclear if 'Unknown' meant unknown or no active treatment. The most affluent patients were more likely to have a registered 'Yes', which is likely to reflect that they were more likely to undergo treatment than the most deprived patients. Patients with an 'Unknown' registration had a poorer prognosis which may indicate that they received no active treatment.

Information bias may also occur if follow-up is incomplete. In study II, based on data from South East England, complete follow-up was available regarding vital status (alive, emigration, or dead). In the Swedish studies there was complete follow-up data on all patients with information based on vital status, and cause of death information retrieved from the Cause of Death Register. The reliability of death certificates for prostate cancer patients has been shown to be high [160]. However, it cannot be excluded that the validity of cause of death information is lower for the elderly, and particular among old patients with severe comorbidity burden. Thus, the validity may vary between age groups.

In study I, we observed a lower diagnostic intensity in lung cancer patients with low education. Thus, some patients with advanced disease might have been misclassified as having early stage disease, which is known as the Will Rogers phenomenon [161]. Inaccurate staging may have led to a poorer stage-specific survival for the most disadvantaged patients.

Confounding is defined as the influence of factors that are associated with the exposure and in themselves predict the likelihood of the outcome, but that are not intermediate steps in the pathway from exposure to outcome [148]. Lack of relevant information on confounding factor is common in retrospective studies. In the studies included in the present thesis information was available on potential confounding factor such as age at diagnosis, performance status, comorbidity and smoking history. Furthermore, we had information on clinical characteristics and planned or received initial treatment. However, these factors may also be intermediate steps in the pathway between socioeconomic status and survival, and thus it is unclear whether adjustment for these factors always is appropriate. Nonetheless, they might help to explain the survival difference between patients with low and high socioeconomic status. In study II, we calculated the contribution of each covariate on the relative change of the hazard ratio between the most deprived and the most affluent patients. With that approach, the most important contribution was found for initial treatment. Furthermore, analyses were stratified on stage at diagnosis and on treatment decisions to minimize possible confounding by indication.

7.1.2 Precision

Precision is defined as the degree to which a measurement is free of random error [148]. High precision of estimates makes chance a less likely explanation of the findings. Sample size, prevalence of exposure and extent of exposure misclassification are important determinants of precision. We considered a significance level of five percent in all studies, and used confidence intervals and p-values as a measure of the precision of our results. A narrow confidence interval implies a small variability in the estimate, and if the confidence interval did not include the null value (or one with odds or hazard ratios) it is unlikely that the findings will be the result of chance. The significance testing should be considered as a measure of chance, and not a proof of association. When several associations between exposure and outcome are addressed simultaneously, the potential role of chance in producing a particular result should not be ignored. There is also a possibility that null results will be due to chance, and that associations between an exposure and an outcome existed that we did not have the statistical power or appropriate tools to discover. While studies in the present thesis included virtually all incident cancer cases during the period under study, the interpretation of results in some subgroups may have been hampered by a small number of events.

7.1.3 External validity

External validity addresses the ability to generalize the studies to other settings [148]. Assuming that bias, confounding and the roles of chance have not seriously affected our results we can assess the applicability of our findings to other populations. The studies included in the present thesis were all based on population based data, and all included men and women residing in well-defined regions with similar health care systems and quality of care. However, the generalizability of our results may be limited by effect modification. An effect modification occurs when the effect of an exposure varies in different subgroups of the population. In study I and II, we observed varied associations by different stages at diagnosis. Thus, we cannot generalize the observed social differences in survival in early stage disease to any other population without information on stage at diagnosis. Furthermore, in the first study, immigrants were excluded which makes it more difficult to generalize the results to regions in Sweden where the proportion of immigrants is high. Also, the interpretations of the results from Study II, based on data from South East England, may not be applicable to other regions of England. Study III and IV included prostate cancer patients from the whole of Sweden, and the results should thus be applicable to all men in Sweden. Because of national differences between health care systems, results from this thesis may not be applicable to patient groups managed in other countries.

7.2 Main findings

7.2.1 Study I and II: Socioeconomic status and lung cancer

We found evidence of social differences in the clinical management and survival in patients diagnosed with lung cancer both in South East England (Study II) and in central Sweden (Study I). In central Sweden, we observed social variations in waiting time from referral to date of diagnosis and higher diagnostic intensity among patients with high education. In both the Swedish and the English study, socioeconomic status was associated with comorbidity burden. We found no evidence of social differences in stage at diagnosis in either study. However, in both settings, there were social variations in treatment intensity, most pronounced in early stage disease. In the Swedish study, we found social differences in lung cancer survival that were restricted to women in early stage disease. The English study found social gradients in survival in both early stage and advanced disease in both sexes. Differences in early stage survival remained throughout follow-up, whereas in advanced disease, variations were confined to the period immediately after diagnosis.

Findings from a British study showed that older age and being unmarried were factors associated with longer diagnostic delays in lung cancer [162]. A recent Danish population based study documented associations between level of education and time between referral and diagnosis [79], findings which corroborate with our Swedish results [163]. While waiting time may not affect prognosis, delays are likely to be associated with anxiety and stress. It has been suggested that multidisciplinary management can reduce delays, particularly with regard to the time between referral and initial treatment [164].

In 2001, Brewster et al. reported that the most deprived patient group with non-small cell lung cancer (NSCLC) were more likely to be diagnosed with localized disease [78], while no such social differences in stage at diagnosis were observed in a large population based study in Canada [77], findings which supports our results. However, Danish investigators reported that lung cancer patients with high education were less likely to be diagnosed with stage IIIB-IV disease [79], which is in line with results from a study from United States [165]. We found that patients with low socioeconomic status were more likely to have co-existing disease, which is supported by findings from Denmark [79], the Netherlands [45] and a Scottish study [166]. Also, in accordance with our results, the Danish study found that patients with severe comorbidity were more likely to be diagnosed with early stage disease which may reflect that the lung cancer was detected in the course of seeking medical care for other conditions.

In accordance with results from earlier studies conducted in United States and England, we found evidence of variations in management by socioeconomic status [85 167-170]. In early stage disease, we observed social gradients in the likelihood to undergo surgical resection, independent of calendar period, sex, age, histology, smoking history and performance status in the Swedish study, and sex, age, and comorbidity burden in the English study. While performance status and comorbidity were taken into account in the analyses, we cannot exclude that poorer general health and surgical risks in the most deprived groups influenced the choice of treatment [171]. In our studies, socioeconomic status was not statistically

significant associated with the likelihood of receiving radiotherapy, but it was in regard to receive on chemotherapy. An earlier study conducted in South East England found a significant social gradient in that chemotherapy was more frequently used in the highest socioeconomic groups, which corresponds to result from a study in United States [167 172]. Another population based study found that patients with high education were more likely to receive radiotherapy than to undergo surgery [173].

Our findings of social variations in lung cancer survival are supported by some [72 88 89 174 175], but not all investigators [40 176]. We found no differences in crude survival among Swedish lung cancer patients when number of persons in the household was used as indicator of social support, results which are supported by at least one other lung cancer study, in which marital status was used as an indicator for social support [177]. When using level of education and a deprivation index as socioeconomic indicators, we observed the largest social differences in early stage disease, supporting the notion that the role of socioeconomic factors is most important for cancer sites with good prognoses where treatment decisions can prolong survival [178]. In the Swedish study, the social inequalities in survival observed among women in early stage were independent of age at diagnosis, histology, performance status, smoking history and treatment factors. In the English study, observed gradients in cancer survival were independent of sex, age at diagnosis, comorbidity, and treatment. Furthermore, detailed analysis of the English data revealed that variations in treatment between the most deprived and the most affluent patients contributed most to the social differences in survival.

To our knowledge, our English study is the first that presents both absolute and relative measures between socioeconomic groups throughout follow-up. In early stage NSCLC, the gap in mortality rates and survival between the most deprived and the most affluent group persisted during follow-up, while in more advanced disease, no social differences were seen five months post diagnosis. Social differences in short-time survival have been previously been reported for colorectal patients in England [179]. It appears unlikely that these findings could be attributed to the registration system in England, i.e. variations between social groups. The observed social variations in lung cancer survival may reflect social differences with regard to the tumor and host characteristics as well as access to care provided by the health care system.

7.2.2 Study III: Socioeconomic status and prostate cancer

In Study III, we demonstrated that men with high socioeconomic status diagnosed with high risk prostate cancer more often underwent an extensive work-up, received active treatment and had better outcomes, compared to men with low socioeconomic status. A bone scan was performed more often among white-collar workers. The likelihood of intention to treat, to receive curative treatment and to undergo radical prostatectomy, was also more common in this group. In the subgroup of men with no signs of metastatic disease that received curative treatment, higher white-collar workers had a lower prostate cancer and all-cause

mortality following adjustment for calendar period, age at diagnosis, clinical characteristics and comorbidity.

Results from several epidemiological studies show that the increasing incidence of prostate cancer in the recent decades reflect a more wide spread use of prostate specific antigen (PSA) testing [180 181]. In 2005, 28 percent of incident prostate cancer cases in Sweden were detected based on the PSA test, while the corresponding proportion in 2009 was 42 percent [65]. The trend towards early detection of prostate cancer has led to efforts to identify men for whom bone scan can be omitted [182-184]. However, there will always be a certain proportion of patients that harbor bone metastases at first diagnosis [182 185 186]. In patients diagnosed with high risk prostate cancer (defined as clinical T3 tumor, and/or Gleason score 8-10, and/or PSA 20-50 ng/mL), guidelines, including those in Sweden, recommend a metastatic work-up [113 187].

A bone scan has a high accuracy of detecting metastatic disease in patients with high risk prostate cancer [113], but is an expensive and time-consuming method of imaging. To our knowledge, our study is the first that has reported social variations in the likelihood of undergoing bone scan following a prostate cancer diagnosis, differences which remained after adjustment for calendar period, age at diagnosis, clinical characteristics and comorbidity. However, our study lacked information on symptoms, such as back pain, that suggest the presence of metastases and that therefore justify performing a bone scan. Thus, it cannot be excluded that our findings reflect differences in reporting symptoms between socioeconomic groups. Moreover, it should be acknowledged that even with a negative result from the bone scan, some high risk patients might still harbor skeletal metastases that remain undetected by conventional scintigraphy [188-190].

In patients with high risk prostate cancer free of metastases, decision regarding curative treatment should be based on the patient's general health and life expectancy, rather than the chronological age [191]. We found that higher white-collar workers were more likely to be treated with curative intent, than blue-collar workers [192]. Social variations in treatment have previously been reported in studies conducted in Switzerland [120], the United States [193] and the United Kingdom [118]. However, none of these studies included information on comorbidity or focused on high risk prostate cancer. The addition of local radiotherapy to endocrine therapy has been shown to reduce the ten year prostate cancer specific mortality by 50 percent [194]. However, no randomized trial has evaluated the effect of radiotherapy on radical prostatectomy in high risk disease. Observational studies have found that both treatment modalities have potential benefits and toxicities that must be taken into consideration in relation to the patient's general health status and clinical characteristics [195]. We found that higher white-collar workers were more likely to undergo radical prostatectomy than radiotherapy, independent of calendar period, age at diagnosis, clinical characteristics and comorbidity. Many clinically prostate tumors categorized as high risk are pathologically confined to the prostate, which may have been the case in the same patients that underwent radical prostatectomy. Furthermore, patients with high socioeconomic status may be more likely to accept the risks associated with surgical resections [196].

In men who underwent curative treatment and who were free of metastatic disease as determined by a bone scan, higher white-collar patients had both a lower all-cause mortality, but also a lower prostate cancer specific mortality than blue-collar workers [192]. Social gradients in survival have previously been observed both for prostate cancer specific and overall survival [118 120 193]. However, no earlier studies have found these gradients in high risk prostate cancer. Results from previous studies have demonstrated that positive surgical margins in radical prostatectomy affect prostate cancer specific survival [197]. Similarly, administrative techniques and dosimetry in radiotherapy, both of which are independent quality control indicators, are known to predict biochemical failure and the likelihood to develop distant metastases [198 199]. The social difference in survival after therapy may thus be explained by clinical factors not evaluated in the present study, such as biopsy tumor burden. Finally, since we observed social differences in initial treatment, it can also be hypothesized that social variations exist with regard to subsequent treatment, which we were unable to explore.

7.2.3 Study IV: Comorbidity and prostate cancer

In study IV, we found that patients diagnosed with prostate cancer with severe comorbidity were more often diagnosed with low risk prostate cancer and were less likely to receive curative treatment compared to patients with no record of co-existing disease. Following adjustment for calendar period, age at diagnosis and clinical characteristics, patients with severe comorbidity had a higher all-cause and competing cause mortality. In analyses of conditional prostate cancer mortality, i.e. analyses given no death due to competing causes, men with severe comorbidity had higher prostate cancer mortality, a finding which was most pronounced in men with more advanced prostate cancer.

Our finding of a lower proportion of low risk disease in patients with severe comorbidity reflects, in all likelihood, a low screening intensity in this group. Several studies have indicated that men diagnosed by PSA testing are younger, healthier and more likely to have a high socioeconomic status than the background population in the same age groups [45], factors that are all associated with a lower comorbidity burden prior to the prostate cancer diagnosis.

Severe comorbidity influences quality of life and life expectancy. Curative treatment such as radical prostatectomy is usually performed only in men with a life expectancy of more than ten years [200]. Because of the natural history of low risk prostate cancer, the majority of patients will not die from their disease within 10 to 15 years from diagnosis [201 202]. We found that the majority of patients with low risk disease and severe comorbidity were put on surveillance. However, almost one fifth (18.3%) of men with low risk disease and severe comorbidity underwent radical prostatectomy, that is associated with a risk of morbidity that can significantly affect quality of life [203-205]. It has previously been reported that men with low risk prostate cancer are often over treated [206], and that men with severe comorbidity and low risk prostate cancer should be considered conservative management, given their exceedingly high risk of death from other causes [207]. However, a study based on the NPCR of Sweden

concluded that 30-days mortality was very low following radical prostatectomy in localized prostate cancer patients [208].

Alibhai pointed out that in men who receive Gonadotropin-releasing hormone (GnRH), the toxicity will be higher in patients with severe comorbidity [209 210]. However, the use of GnRH as the primary choice of treatment in patients with localized disease has decreased in Sweden over time, results which are essentially in accordance with data in United States [209 211]. In the present study, surveillance or hormonal treatment was the treatment of choice in all clinical risk groups in men with severe comorbidity, which indicates that general guidelines are adhered to and that comorbidity is considered in treatment decisions [212]. Earlier results have also indicated that comorbidity seems to be integrated into treatment decisions for prostate cancer [213-216]. However, results from some studies have suggested that patient age and the clinician's experience are the primary determinants for treatment decisions, and not comorbidity burden [217 218].

In the present study, we found an increased risk of all-cause and competing cause mortality, but not prostate cancer specific mortality in patients with severe comorbidity in all clinical risk groups. Our findings were expected, and several other investigators have found associations between comorbidity and mortality in prostate cancer patients [158 207 219-222]. The relative gap in all-cause and competing cause mortality between patients with no record of comorbidity and severe comorbidity was largest in low risk disease, which is in line with recent data from the United States [223]. In a competing risk setting, a randomized trial showed no statistically significant increased risk of prostate cancer mortality in patients with at least one severe comorbidity [224], which also supports our findings.

The association between comorbidity and all-cause and competing cause mortality is likely to be explained primarily by co-existing diseases. However, it cannot be excluded that the prostate cancer related treatment also negatively influenced mortality [225 226]. We observed increased conditional prostate cancer mortality in patients with severe comorbidity. Stratified analyses revealed that the gap in conditional prostate cancer mortality between patients with severe comorbidity and free of comorbidity was most pronounced in more advanced prostate cancer.

7.3 General discussion and future perspectives

Taken together, the result of the present thesis shows that socioeconomic status influences not only clinical management, but also survival in patients diagnosed with lung cancer both in central Sweden and South East England, as well as in patients with prostate cancer in Sweden, using different indicators for socioeconomic status. Furthermore, comorbidity burden influenced both treatment decisions as well as outcomes in prostate cancer. The mechanisms underlying socioeconomic differences in management and survival remain unclear, but may be discussed in relation to at least three dimensions: factors relating to the tumor, the host and the health care system.

Tumor characteristics include both biological features of a tumor and stage at diagnosis. The histological type is an important biological feature of a tumor and may also be a prognostic factor. For example, lung cancer patients diagnosed with small cell lung cancer experience poorer survival than patients diagnosed with non-small cell lung cancer. Small cell lung cancer has been shown to be strongly associated with tobacco smoking, which is more common in lower socioeconomic groups. It has been suggested that part of the lower survival observed in lower socioeconomic groups may be explained by differences in histological subtypes. In study I, the study population was restricted to patients with non-small cell lung cancer, whereas in study II, both non-small cell and small cell lung cancer were included. Thus, the observed social differences in survival in more advanced stage lung cancer in study II, but not in study I, may be related to distribution of histological subtypes. Prostate cancer is histologically a more homogenous cancer form with more than 99 percent of cases being adenocarcinomas. A more advanced stage at diagnosis has been put forward as a key explanation for a poorer cancer survival in low socioeconomic groups. However, we found no evidence of social differences in stage at diagnosis in lung cancer. Study III was restricted to high risk prostate cancer, but no differences in clinical subgroups were observed between social groups. In conclusion, it seems unlikely that the observed social differences in survival could be fully explained by lead time bias, if stage at diagnosis and clinical subgroups are used as indicators for lead time.

Host characteristics represent another possible explanation for social differences in survival. Deprived patient groups with poor health may have an impaired host resistance, facilitating rapid tumor growth and spread. Also, life-style factors that have been associated with low socioeconomic status include physical inactivity, poor nutritional status, obesity, alcohol consumption and tobacco smoking. All these factors may be associated with poorer outcomes. Similar to findings in earlier studies, we found that patients with low socioeconomic status had a higher comorbidity burden at diagnosis or a poorer performance status at date of initial treatment. In our studies, adjustment for comorbidity or performance status did not eliminate the survival differences according to socioeconomic status. Also survival differences remained when analyses were restricted to patients with no record of comorbidity. Tobacco smoking leads to a poorer health status, but was not quantifiable in our comorbidity score. In Study I, social inequalities in survival in early stage lung cancer remained following adjustment for self-reported tobacco smoking. Stressful life events, and lack of social support have also been found to be more common among groups with low socioeconomic status, but the possible prognostic role of these factors in lung and prostate cancer patients remains incompletely understood. We found no differences in survival among Swedish lung cancer patients when the number of persons in the household was used as indicator for social support. The observed social differences in survival in the present thesis could not be fully explained by host characteristics such as comorbidity burden, performance status and smoking history.

The health care system represents a key determinant for cancer outcomes. We found evidence of social differences in both diagnostic and treatment intensity among lung and prostate cancer patients. Social differences in treatment explained most of the observed inequalities in lung cancer survival in study II. Possible explanations include differences in rapport between the physician and the patient, demands and expectations from the patient

and the communication skills of both parties. There may also be social differences in acceptance of compliance with treatments such as adjuvant therapies. Economic barriers to accessing a cure are unlikely to explain the findings in our Swedish studies. In conclusion, our findings may reflect aspects of physician-patient interaction and a subtle bias towards more action on behalf of the physicians when managing high socioeconomic status patients.

Taken together, the results of the present thesis show that social differences exist in the clinical management and survival of patients diagnosed with lung cancer in central Sweden and in South East England, as well as in patients diagnosed with prostate cancer in Sweden. Furthermore, we found that comorbidity was considered in management decisions and influenced survival in prostate cancer. Our findings raise the importance of continuous monitoring of quality and equality of cancer care using information available in quality registers on cancer and in other health care databases. Equality in cancer management and survival needs to be addressed, not only in relation to socioeconomic status, but also with regard to ethnicity, age and region of residence.

Also, further research is needed to improve the understanding of the relative contribution of tumor characteristics, the host, and the health care provider, that can explain the observed social differences in management and survival. In this context, more detailed information on comorbidity would be of interest both in relation to socioeconomic status and to the role of co-existing disease.

8 CONCLUSIONS

- We found evidence of a social gradient in the clinical management and survival in patients diagnosed with lung cancer both in central Sweden and in South East England. Both shorter waiting time from referral to date of diagnosis and a higher diagnostic intensity were observed in lung cancer patients with high socioeconomic status, while no social differences in stage at diagnosis were observed in Sweden or England.

- Lung cancer patients with high socioeconomic status were more likely to undergo an active treatment, most pronounced in early stage disease. The observed social inequalities in lung cancer survival were most pronounced in early stage disease, and could not fully be explained by comorbidity burden and smoking history. In South East England, the social gradients in survival in early stage disease remained throughout follow-up, whereas in advanced disease, variations in survival were confined to the period immediately after diagnosis.

- White-collar workers diagnosed with high risk prostate cancer underwent more often an extensive work-up, received active treatment and had better outcomes compared with blue-collar workers. A bone scan was performed more often among white-collar workers. The likelihood of intention to treat, reception of curative treatment and radical prostatectomy treatment was also more common among these patients. In the subgroup of men with no signs of metastatic disease that received curative treatment, higher white-collar workers had a lower all-cause as well as prostate cancer specific mortality.

- Patients diagnosed with prostate cancer with severe comorbidity were less often diagnosed with low risk prostate cancer and received less curative treatment than to patients with no co-existing disease. Patients with severe comorbidity had a higher all-cause and competing cause mortality, but not prostate cancer specific mortality. In analyses given no death due to competing causes, men with severe comorbidity had higher prostate cancer mortality, foremost in men with more advanced prostate cancer.

9 SWEDISH SUMMARY (Svensk sammanfattning)

Resultat från epidemiologiska studier från olika delar av världen har pekat på förekomsten av sociala skillnader i canceröverlevnad. Det är känt att många patienter vid sidan av sin cancersjukdom också lider av andra sjukdomar. Studierna i denna avhandling undersöker eventuella skillnader mellan socioekonomiska grupper avseende handläggningsintensitet och överlevnad bland patienter med lungcancer i Mellansverige och sydöstra England, och patienter med högrisk prostatacancer i Sverige. Dessutom studeras om samsjuklighet hos svenska prostatacancerpatienter påverkar val av behandling och dödlighet.

Studierna i avhandlingen baserades på information från det Regionala Lungcancerregistret i Uppsala-Örebroregionen, Thames cancerregister i Sydöstra England och forskningsdatabasen PCBaSe Sweden, en informationskälla baserad på Nationella Prostatacancerregistret med länkningar till bl.a. LISA-databasen, Cancerregistret, Patientregistret och Dödsorsaksregistret. Utbildningsnivå, ett Jämlikhetsindex, och ett socioekonomiskt index baserat på yrke användes som de huvudsakliga indikatorerna för socioekonomisk status. I syfte att skatta grad av annan sjukdomsbörda användes Charlson´s komorbiditetsindex. Samband mellan socioekonomisk status, komorbiditet, handläggning och risken för död analyserades med bland annat logistisk regression och överlevnadsanalys.

Vi fann förekomst av sociala skillnader avseende väntetid och diagnostisk intensitet bland patienter med lungcancer i Mellansverige. Inga sociala gradienter i stadium vid diagnos observerades vare sig i Mellansverige eller Sydöstra England. I båda regionerna erhöll de mest privilegierade patienterna med lungcancer oftare kurativ syftande behandling och hade även en bättre överlevnad, något som var speciellt tydligt bland patienter med lungcancer i tidiga stadier. Vi observerade även sociala skillnader i handläggning av män med högrisk prostatacancer. Sannolikheten att genomgå skelettscintigrafi, erhålla kurativt syftande behandling och opereras var högre bland män med hög socioekonomiskt status, vilka även hade en lägre dödlighet i sin prostatacancersjukdom.

Prostatacancerpatienter med hög samtidig annan sjukdomsbörda erhöll i mindre utsträckning behandling i kurativt syfte, och hade en högre total dödlighet och av andra orsaker, men inte avseende död i prostatacancer. Däremot, givet att prostatacancerpatienterna inte avled av andra orsaker, var dödligheten högre i gruppen med hög annan sjukdomsbörda jämfört med gruppen utan känd samsjuklighet.

Sammanfattningsvis visar våra resultat på förekomsten av socioekonomiska skillnader i handläggning och överlevnad för patienter med lungcancer i Mellansverige och Sydöstra England, och bland svenska patienter med högrisk prostatacancer av högrisktyp. Resultaten visar även att komorbiditet både påverkar val av behandling och dödlighet bland prostatacancerpatienter. Behandlingsmönster och överlevnad bland de mest privilegierade cancerpatienterna visar vad som är uppnåbart och bör utgöra en minimistandard för samtliga patienter oavsett bakgrund.

10 ACKNOWLEDGEMENTS

The studies behind this thesis were carried out at the Department of Medical Epidemiology and Biostatistics at the Karolinska Institutet, Sweden during August 2008, to February 2012. The doctoral period has been an incredible journey, and I am grateful for all valuable help that the following persons have given me during this research:

Mats Lambe, M.D., Professor of Cancer Epidemiology, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet; my principal supervisor, thank you for introducing a new world of doctoral studentship to me, for your encouragement, for all great scientific discussions, and your endless support during these years. I also wish to thank you for introducing me to several challenging fields of cancer epidemiology, and your support led me to become an independent researcher with teamwork skills.

Lars Holmberg, M.D., Professor of Cancer Epidemiology, Department of Cancer Epidemiology, King's College; my co-supervisor, who, with his long experience of cancer epidemiology, is a tower of strength to lean on for any doctoral student. Thank you for mediating contact with researchers in England.

Carol Tishelman, R.N., Professor of Nursing, Department of Learning, Informatics, Management and Ethics, Karolinska Institutet; my co-supervisor, for excellent skills in nursing and lung cancer, guidance through the research process, constructive criticism and for believing in my capacity.

Pär Stattin, M.D., Professor of Urology, Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University; co-author, for always being available and supportive during the doctoral period, and for inviting me to your research environment and conferences. Thank you for sharing your extensive knowledge and experience not only in the broad field of prostate cancer research, but also in cancer epidemiology.

Henrik Møller, BA., B.Sc., M.Sc., DM., FFPH., Professor of Cancer Epidemiology at Thames Cancer Registry, King's College; co-author, for inviting me as a guest researcher at the Thames Cancer Registry, and for sharing your vast knowledge in statistics and cancer epidemiology. It has been a privilege to work with you, and I hope that we can extend our collaboration.

Henrik Grönberg, MD., Professor of Urology, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet; for accepting me as a doctoral student at the Department.

Hans Garmo, Ph.D., Department of Cancer Epidemiology, School of Medicine, King's College; co-author, an open-minded mathematical statistician and a truly great scientist in the field of cancer research.

Johan Hallqvist, M.D., Professor of Social Medicine, Department of Medicine, Uppsala University; thank you for sharing your great knowledge in causal inference and social epidemiology.

Gunnar Wagenius, M.D., Associate Professor of Oncology, Karolinska University Hospital; co-author, for your expertise in the broad field of lung cancer research, and for interesting conferences, regional and national meetings.

Jan Adolfsson, M.D., Associate Professor of Urology, Karolinska Institutet; co-author, for your valuable input not only in this thesis, but also in other epidemiological studies, looking forward to extend the collaboration in the future.

My co-authors, **Sonja Eaker**, Ph.D., Uppsala University, **Margreet Lüchtenborg**, Ph.D., Thames Cancer Registry, King's College; **Karen M. Linklater**, Information Analyst/Researcher, Thames Cancer Registry, King's College; **Michael D. Peake**, M.D., Senior Lecturer in Respiratory Medicine, Glenfield Hospital; **David Robinson**, M.D., PhD, Ryhov County Hospital and **Ola Bratt**, M.D., Associate Professor of Urology, Lund University, for all your valuable help during the research period, it has been a pleasure to collaborate with you.

Annette Wigertz, M.D., Ph.D., Regional Cancer Center; for interesting epidemiological discussions and who lent me some of your valuable time by reading and comment on my thesis.

Therese Andersson, M.Sc. in mathematics, doctoral researcher, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet; for sharing excellent skills in biostatistics, for reading my manuscripts and for comments on the statistical part in my thesis.

Fredrik Sandin, M.Sc. in mathematics, Regional Cancer Center; for stimulating conversations who never said no to fruitful discussions about data management and biostatistics.

Jerzy Leppert, M.D., Professor, Uppsala University, **Leif Bergkvist**, M.D., Professor, Uppsala University, and **Mats Enlund**, M.D., Associate Professor, Uppsala University; for inviting me to your research team and for an excellent course in scientific writing in France.

Inna Feldman, Ph.D., Community Medicine, Uppsala County Council; introduced me to epidemiology and public health and I am looking forward for more fruitful collaborations.

Paul Gratwick, for linguistic reading.

All colleagues at the Department of Medical Epidemiology and Biostatistics and the Department of Environmental Medicine, and all the **doctoral students** at the Health Care Sciences Postgraduate School for fruitful discussions during coffee breaks, Journal Clubs and meetings, and the **administration staff** at the Department of Medical Epidemiology and Biostatistics, without you would have been much more difficult.

The Health Care Sciences Postgraduate School for financial aid and general support during my entire doctoral period. It has been a privilege to take part in the activities, and especially I would like to thank Associate Professor **Ingeborg van der Ploeg**, Professor **Lena von Koch**, and **Åsa Trulsson** for all valuable help during this journey.

I would like to thank all my **former** and **present colleagues** at the **Regional Cancer Center** in the Uppsala/Örebro region, it has been a pleasure to work with you since I started in May 2007. This thesis would not be possible without your endless contribution to quality control and your vast expertise in the management of cancer patients.

I would like to thank my old friends outside the field of medical research, **Linus Bäcklund** with his wife, **Olle Tillman**, and **Fredrik Ericsson** with his fiancée for great times during the years. I promise to spend more time with you guys when this journey is over.

My mother **Birgitta** and father **Lars Berglund**, Ph.D, for your support and never ending faith in me. My sister **Emma Berglund**, R.N. with her boyfriend for your support, and my mother-in-law **Kata Botic**, and my wife's sister and family for encouragement and helping out with keeping the number of VAB days to a minimum.

Most importantly I express my gratitude and thanks to my wife. **Snjezana Berglund** for your endless love, support and care. Thank you for your patience in listening to my issues, and at the same time being a mother to two children. Undoubtedly, without your support and encouragement I would not have been able to finalize my thesis. Volim te Miska!

To my wonderful two daughters, **Saga** and **Axelia Berglund**, you both have brought joy, pleasure and real happiness into my life in ways that are impossible to describe.

Financial support, research grants and travel scholarships were granted by:

The Health Care Sciences Postgraduate School
Swedish Council for Working life and Social Research
Swedish Cancer Society
Swedish Research Council

Thank you,

Anders Berglund
January 2012, Stockholm, Sweden

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